Sunshine Act Meetings

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This section of the FEDERAL REGISTER contains notices of meetings published under the "Government in the Sunshine Act" (Pub. L. 94-409) 5 U.S.C. 552b(e)(3).

CONTENTS

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FEDERAL DEPOSIT INSURANCE CORPORATION

Pursuant to the provisions of the "Government in the Sunshine Act" (5 U.S.C. 552b), notice is hereby given that at 10:20 a.m. on Monday, June 23, 1986, the Board of Directors of the Federal Deposit Insurance Corporation met in closed session, by telephone conference call, to consider the following matters:

(A) Application of the Connecticut National Bank, Hartford, Connecticut, for consent to purchase certain assets of and assume the liability to pay deposit made in the Cromwell (Cromwell Commons), Wallingford (Main Street), and Meriden (West Main Street), Connecticut, offices of Jefferson Federal Savings and Loan Association, Meriden, Connecticut, a non-FDIC-insured institution.

(B) Application of the New Haven Savings Bank, New Haven, Connecticut, an insured mutual saving bank, for consent to purchase certain assets of and assumed the liability to pay deposits made in the Middletown and Milford, Connecticut, offices of Jefferson Federal Savings and Loan Association, Meriden, Connecticut, a non-FDIC-insured institution, and for consent to establish those two offices as branches of The New Haven Savings Bank.

(C) Application of The Liberty Bank for Savings, Middletown, Connecticut, an insured mutual savings bank, for consent to purchase certain assets of and assume the liability to pay deposits made in the Cromwell (Main Street), Connecticut, office of Jefferson Federal Savings and Loan Association, Meriden, Connecticut, a non-FDIC-insured institution, and for consent to establish that office as a branch of The Liberty Bank for Savings.

(D) Application of Home Bank and Trust Company, Meriden, Connecticut, an insured State nonmember bank, for consent to purchase certain assets of and assume the liability to pay deposits made in the New Haven, Connecticut, office of Jefferson Federal Savings and Loan Association, Meriden, Connecticut, a non-FDIC-insured insitituion, and for consent to establish that office as a branch of Home Bank and Trust Company.

(E) Application of Citytrust, Bridgeport, Connecticut, an insured State nonmember bank, for consent to purchase certain assets of and assume the liability to pay deposits made in the Wallingford (Turnpike Road), Connecticut, office of Jefferson Federal Savings and Loan Association, Meriden, Connecticut, a non-FDIC-insured institution, and for consent to establish that office as a branch of Citytrust.

(F) Application of Colonial Bank, Waterbury, Connecticut, an insured State nonmember bank, for consent to purchase certain assets of and assume the liability to pay deposits made in the Southington, Connecticut, office of Jefferson Federal Savings and Loan Association, Meriden, Connecticut, a non-FDIC-insured institution, and for consent to establish that office as a branch of Colonial Bank.

At that same meeting, the Board also considered a personnel matter.

In calling the meeting, the Board determined, on motion of Chairman L. William Seidman, seconded by Director C.C. Hope, Jr. (Appointive), concurred in by Director Robert L. Clarke (Comptroller of the Currency), that Corporation business required its consideration of the matters on less than seven days' notice ot the public; that no earlier notice of the meeting was practicable; that the public interest did not require consideration of the matters in a meeting open to public observation; and that the matters could be considered in a closed meeting pursuant to subsections (c)(2), (c)(6), (c)(8), and (c)(9)(A)(ii) of the "Government in the Sunshine Act" (5 U.S.C. 552b(c)(2), (c)(6), (c)(8), and (c)(9)(A)(ii)).

Dated: June 23, 1986.

Federal Deposit Insurance Corporation.

Hoyle L. Robinson,

Executive Secretary.

[FR Doc. 86-14530 Filed 6-24-86;11:14 am]

BILLING CODE 6714-01-M

2

FEDERAL DEPOSIT INSURANCE CORPORATION

Pursuant to the provisions of the "Government in the Sunshine Act" (5 U.S.C. 552b), notice is hereby given that at 4:57 p.m. on Friday, June 20, 1986, the Board of Directors of the Federal Deposit Insurance Corporation met in closed session, by telephone conference call, to adopt: (1) A resolution (a) making funds available for the payment of insured deposits made in The American Bank, Alma, Wisconsin, which was closed by the Commissioner of Banking for the State of Wisconsin on Friday, June 20, 1986; (b) accepting the bid of Bank of Alma, Alma, Wisconsin, a newly-chartered State nonmember bank, for the transfer of the insured and fully secured or preferred deposits of the closed bank; (c) designating Bank of Alma, Alma, Wisconsin, as the agent for the Corporation for the payment of insured and fully secured or preferred deposits of the closed bank; and (2) an Order approving the applications of Bank of Alma, Alma, Wisconsin, for Federal deposit insurance, for consent to purchase certain assets of and assume the liability to pay deposits made in The American Bank, Alma, Wisconsin, and for consent to establish the two branches of The American Bank as branches of Bank of Alma.

In calling the meeting, the Board determined, on motion of Director C.C. Hope, Jr. (Appointee), seconded by Mr. Dean S. Marriott, acting in the place and stead of Director Robert L. Clarke (Comptroller of the Currency), that Corporation business required its consideration of the matters on less than seven days' notice to the public; that no earlier notice of the meeting was practicable; that the public interest did not require consideratin of the matters in a meeting open to public observation; and that the matters could be considered in a closed meeting pursuant to subsections (c)(8), (c)(9)(A)(ii), and (c)(9)(B) of the "Government in the Sunshine Act" (5 U.S.C. 552b(c)(8), (c)(9)(A)(ii), and (c)(9)(B)).

Dated: June 23, 1986.

Federal Deposit Insurance Corporation.

Hoyle L. Robinson,

Executive Secretary.

[FR Doc. 86-14587 Filed 6-24-86; 3:17 pm]

BILLING CODE 6714-01-M

3

FEDERAL MARITIME COMMISSION

TIME AND DATE: 10:00 a.m., June 25, 1986.

PLACE: Hearing Room One, 1100 L Street, NW., Washington, D.C. 20573

STATUS: Closed.

MATTER TO BE CONSIDERED:

1. The Use of High-Cube Containers in Japan.

CONTACT PERSON FOR MORE INFORMATION: John Robert Ewers, Secretary, (202) 523–5725.

John Robert Ewers,

Secretary.

[FR Doc. 86–14590 Filed 6–24–86; 3:18 pm]

BILLING CODE 6730–01–M

4

FEDERAL RESERVE SYSTEM

TIME AND DATE: 10:00 a.m., July 2, 1986.

PLACE: Marriner S. Eccles Federal Reserve Board Building, C Street entrance between 20th and 21st Streets, NW., Washington, D.C. 20551.

STATUS: Closed.

MATTERS TO BE CONSIDERED:

1. Proposed use of credit cards for official travel expenses.
2. Personnel actions (appointments, promotions, assignments, reassignments, and salary actions) involving individual Federal Reserve System employees.
3. Any items carried forward from a previously announced meeting.

CONTACT PERSON FOR MORE INFORMATION: Mr. Joseph R. Coyne, Assistant to the board; (202) 452–3204. You may call (202) 452–3207, beginning at approximately 5 p.m. two business days before this meeting, for a recorded announcement of bank and bank holding company applications scheduled for the meeting.

Dated: June 24, 1986.

James McAfee,

Associate Secretary of the Board.

[FR Doc. 86–14594 Filed 6–24–86; 3:58 pm]

BILLING CODE 6210–01–M

5

MERIT SYSTEMS PROTECTION BOARD

Sunshine Act Meeting; Change

"FEDERAL REGISTER" CITATION OF PREVIOUS ANNOUNCEMENT: Vol. 51, No. 115, 21825, June 16, 1986.

PREVIOUSLY ANNOUNCED TIME AND DATE OF MEETING: June 26, 1986, 10:00 a.m.

PLACE: Eighth Floor, 1120 Vermont Avenue, NW., Washington, DC.

STATUS: Open.

CHANGE IN THE MEETING: The hearing scheduled in *Woods* v. *U.S. Customs Service*, MSPB Docket No. PH07528310145, has been postponed until further notice.

CONTACT PERSON FOR ADDITIONAL INFORMATION: Robert E. Taylor, Clerk of the Board, (202) 653–7200.

Dated: June 24, 1986.

Robert E. Taylor,

Clerk of the Board.

[FR Doc. 86–14597 Filed 6–24–86; 4:16 pm]

BILLING CODE 7400–01–M

federal register

Thursday
June 26, 1986

Part II

Office of Science and Technology Policy

Coordinated Framework for Regulation of Biotechnology; Announcement of Policy and Notice for Public Comment

OFFICE OF SCIENCE AND TECHNOLOGY POLICY

Coordinated Framework for Regulation of Biotechnology

AGENCY: Executive Office of the President, Office of Science and Technology Policy.

ACTION: Announcement of policy; notice for public comment.

SUMMARY: This **Federal Register** notice announces the policy of the federal agencies involved with the review of biotechnology research and products. As certain concepts are new to this policy, and will be the subject of rulemaking, the public is invited to comment on these aspects which are specifically identified herein.

DATE: Comments must be received on or before August 25, 1986.

Public Participation: The Domestic Policy Council Working Group on Biotechnology through the Office of Science and Technology Policy, is seeking advice on certain refinements published herein to the previously published proposed coordinated framework for regulation of biotechnology. These new aspects include the Biotechnology Science Coordinating Committee's (BSCC's) definitions for an "intergeneric organism (new organism)" and for "pathogen." These definitions are critical to the coordinated framework for the regulation of biotechnology because they establish the types of the organisms subject to certain kinds of review.

It is the intention of the Domestic Policy Council Working Group on Biotechnology, the Biotechnology Science Coordinating Committee (BSCC), the Department of Agriculture (USDA), the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), the National Science Foundation (NSF), and the Occupational Safety and Health Administration (OSHA) that the policies contained herein be effective immediately. In consideration of comments, modifications, if any, may be published either in a separate notice or as part of proposed rulemaking by the involved agencies.

Information submitted to an agency that is trade secret information or confidential business information should be clearly marked so that it can be accorded the protection provided to such by each respective agency.

ADDRESS: Comments specific to the BSCC definitions or overall comments to the Coordinated Framework for the Regulation of Biotechnology statements should be addressed to: BSCC: Docket #BSCC 0001, Office of Science and Technology Policy, Executive Office of the President, NEOB-Room 5005, Washington, DC 20506.

Comments relating to the policy statements of a particular agency should be sent directly to the agency contact identified at the beginning of the respective agency policy statement.

FOR FURTHER INFORMATION CONTACT: Dr. David T. Kingsbury, Assistant Director for Biological, Behavioral, and Social Sciences, National Science Foundation, 1800 G Street, N.W., Washington, D.C. 20550, (202–357–9854).

Jerry D. Jennings,

Executive Director, Office of Science and Technology Policy

June 18, 1986

Table of Contents

A. Introduction

This notice describes the comprehensive federal regulatory policy for ensuring the safety of biotechnology research and products. Specifically addressed are agency policies that formed part of the previously proposed Coordinated Framework for the Regulation of Biotechnology, published in the **Federal Register** December 31, 1984 (49 FR 50856, hereinafter "the December 84 Notice"). These agency policies build upon experience with agricultural, pharmaceutical, and other commercial products developed by traditional genetic modification techniques.

Existing statutes provide a basic network of agency jurisdiction over both research and products; this network forms the basis of this coordinated framework and helps assure reasonable safeguards for the public. This framework is expected to evolve in accord with the experiences of the industry and the agencies, and, thus, modifications may need to be made through administrative or legislative actions.

The application of traditional genetic modification techniques is relied upon broadly for enhanced characteristics of food (e.g., hybrid corn, selective breeding), manufactured food (e.g., bread, cheese, yogurt), waste disposal (e.g., bacterial sewage treatment), medicine (e.g., vaccines, hormones), pesticides (e.g. *Bacillus thuringiensis*) and other uses. Federal agencies implement an array of laws which seek to ensure the safety of these products. A concise index of these U.S. laws was published in the **Federal Register** November 14, 1985 (50 FR 47174, hereinafter "the November 85 Notice"). These laws are product-specific because they regulate certain product uses, such as foods or pesticides. This approach provides the opportunity for similar products to be treated similarly by particular regulatory agencies.

Biotechnology also includes recently developed and newly emerging genetic manipulation technologies, such as recombinant DNA (rDNA), recombinant RNA (rRNA) and cell fusion, that are sometimes referred to as genetic engineering. While the recently developed methods are an extension of traditional manipulations that can produce similar or identical products, they enable more precise genetic modifications, and therefore hold the promise for exciting innovation and new areas of commercial opportunity.

Concerns were raised as to whether products resulting from the recently developed techniques would pose greater risks than those achieved through traditional manipulation techniques. For example, what might be the possible environmental consequences of the many anticipated agricultural and environmental applications that will take place outside the physical constraints of a contained facility? In particular, the environmental application of genetically engineered microorganisms may elicit concern because they are of microscopic size, and some may be able to reproduce, proliferate, and become established.

The underlying policy question was whether the regulatory framework that pertained to products developed by traditional genetic manipulation techniques was adequate for products obtained with the new techniques. A similar question arose regarding the sufficiency of the review process for research conducted for agricultural and environmental applications.

The Administration, recognizing its responsibility to confront these concerns, formed an interagency working group under the former White House Cabinet Council on Natural Resources and the Environment in the spring of 1984. The working group sought to achieve a balance between regulation

adequate to ensure health and environmental safety while maintaining sufficient regulatory flexibility to avoid impeding the growth of an infant industry.

Upon examination of the existing laws available for the regulation of products developed by traditional genetic manipulation techniques, the working group concluded that, for the most part, these laws as currently implemented would address regulatory needs adequately. For certain microbial products, however, additional regulatory requirements, available under existing statutory authority, needed to be established.

The existing health and safety laws had the advantage that they could provide more immediate regulatory protection and certainty for the industry than possible with the implementation of new legislation. Moreover, there did not appear to be an alternative, unitary, statutory approach since the very broad spectrum of products obtained with genetic engineering cut across many product uses regulated by different agencies.

Because of the rapid growth in the scientific knowledge base, the working group felt strongly that the federal agencies needed to have an interagency mechanism for sharing scientific information related to biotechnology, particularly information on research and product applications submitted to the agencies.

The December 1984 Notice described the regulatory framework envisioned by the working group, and recognizing the evolutionary nature of its development, asked for comments. In summary, the Notice stated that the Food and Drug Administration (FDA) would regulate genetic engineering products no differently that those achieved through traditional techniques. The Environmental Protection Agency (EPA) described existing and proposed new policies for regulating pesticidal and nonpesticidal microorganisms. The Department of Agriculture (USDA) stated that under its different legislative authorities it could broadly regulate genetically engineered plants and animals, and plant and animal pathogens. The Notice also proposed an interagency science coordinating mechanism.

Many comments were received in response to the Notice. These contributed to the refinement of both the regulatory requirements and the interagency science coordination mechanism.

The interagency coordination mechanism, the Biotechnology Science Coordinating Committee (BSCC), discussed in more detail in section C. of this Preamble, came into being while the agencies were still in process of refining their regulatory proposals. Consequently, the BSCC was able to play a helpful role in the formulation of two basic principles: (1) Agencies should seek to adopt consistent definitions of those genetically engineered organisms subject to review to the extent permitted by their respective statutory authorities; and, (2) agencies should utilize scientific reviews of comparable rigor.

The regulatory framework anticipates that future scientific developments will lead to further refinements. Experience with earlier basic scientific research has shown that as the science progressed and became better understood by the public, regulatory regimens could be modified to reflect more complete understanding of the potential risks involved. Similar evolution is anticipated in the regulation of commercial products as scientists and regulators learn to predict more precisely particular product use that require greater or lesser controls or even exemption from any federal review.

This framework has sought to distinguish between those organisms that require a certain level of federal review and those that do not. This follows a traditional approach to regulation. Within agriculture, for example, introductions of new plants, animals and microorganisms have long occurred routinely with only some of those that are not native or are pathogenic requiring regulatory approval. It should be noted that microorganisms play many essential and varied roles in agriculture and the environment and that for decades agricultrual scientists have endeavored to exploit their advantages through routine experimentation and introduction into the environment; and as a rule these agricultural and environmental introductions have taken place without harm to the environment.

B. The Coordinated Framework for the Regulation of Biotechnology

General Comments

This notice includes separate descriptions of the regulatory policies of FDA, EPA, OSHA and USDA and the research policies of the National institutes of Health (NIH), NSF, EPA and USDA. The agencies will seek to operate their programs in an integrated and coordinated fashion and together should cover the full range of plants, animals and microorganisms derived by the new genetic engineering techniques. To the extent possible, responsibility for a product use will lie with a single agency. Where regulatory oversight or review for a particular product is to be performed by more than one agency, the policy establishes a lead agency, and consolidated or coordinated reviews. While this preamble seeks to convey an overview of the coordinated framework, it must be noted that the regulatory requirements are highly technical; reliance only on the simplified summary statements herein could be misleading and, thus, the agency policy statements must be consulted for specific details. In the event that questions arise regarding which federal agency has jurisdiction, an information contact is provided at the beginning of this notice.

While in part certain USDA and EPA requirements are new, the underlying regulatory regimens are not new. Members of the agricultural and industrial communities are familiar with the general requirements under these laws which include the Federal Plant Pest Act, The Plant Quarantine Act, the Toxic Substances Control Act (TSCA), and the Federal insecticide, Fungicide, and Rodenticide Act (FIFRA).

Because this comprehensive regulatory framework uses a mosaic of existing federal law, some of the statutory nomenclature for certain actions may seem inconsistent. Certain laws, such as USDA's Federal Plant Pest Act, require a "permit" before a microorganism pathogenic to plants may be transported or imported. Under other laws such as FIFRA, the agencies "license" or "approve" the use of particular products. TSCA requires a "premanufacturing notification (PMN)". There are also some variations among the agencies in the use of the phrase "genetic enginering." Regardless of the nomenclature, the public should be aware that the reviews conducted by each of the regulatory agencies are intended to be of comparable rigor. Agencies have agreed to have scientists from each other's staff participate in reviews. Each regulatory review will require that the safety, or safety and efficacy, of a particular agricultural or industrial product be satisfactorily demonstrated to the regulatory agency prior to commercialization.

The National Environmental Policy Act (NEPA) imposes procedural requirements on all federal agencies to prepare an analysis prior to making a decision to take any action that may significantly affect the environment. Depending on the characteristics of a proposal, an environmental assessment, or a broader environmental impact statement may need to be prepared in connection with the release of

genetically manipulated organisms. EPA's actions under most of its environmental statutes have been considered to be the functional equivalent of NEPA compliance.

For the handling of microorganisms, agencies of the Department of Health and Human Services have established recommendations for the safe use of infectious agents. The CDC/NIH publication, *Biosafety in Microbiological and Biomedical Laboratories*, describes combinations of standard and special microbiological practices, safety equipment and facilities which are recommended for working with a variety of infectious agents in research laboratories, academic and industrial. The USDA also has issued guidance on other infectious agents.

The NIH has published guidelines for the contained use of DNA organisms in the *NIH Guidelines for Research Involving Recombinant DNA Molecules*, **Federal Register**, May 7, 1986 (51 FR 16958, NIH guidelines). The guidelines recommend physical containment at specific levels for different experiments, and exempt other experiments from containment requirements. However, they recommend Biosafety Level 1, the least stringent level of physical containment, for some "exempt" experiments. For large-scale exempt experiments, the NIH guidelines recommend "Biosafety Level 1-Large-Scale" although following review by the Institutional Biosafety Committee, "some latitude" in the application of these requirements is permitted.

The appropriate large-scale containment requirements for many low risk DNA derived industrial microorganisms will be no greater than those appropriate for the unmodified parental organisms. This concept is discussed further in the Organization for Economic Cooperation and Development (OECD) document, described in the International Aspects section below.

OSHA in its **Federal Register** Notice of April 12, 1984 (50 FR 14468) stated that its authority under the Occupational Safety and Health Act of 1970 (29 U.S.C. et seq.) provides an adequate and enforceable basis for protecting the safety and health of employees in the field of biotechnology and that no additional regulation is necessary. After consideration of comments in the April 1984 notice, OSHA is publishing this policy statement in final form without change.

Product Regulation

Agencies involved with regulating agriculture, foods, medical devices, drugs, biologics and pesticides have had extensive experience with products that involve living organisms in their manufacture and/or ultimate use including releases into the environment for these purposes. By the time a genetically engineered product is ready for commercialization, it will have undergone substantial review and testing during the research phase, and thus, information regarding its safety should be available. The manufacture by the newer technologies of food, the development of new drugs, medical devices, biologics for humans and animals, and pesticides, will be reviewed by FDA, USDA and EPA in essentially the same manner for safety and efficacy as products obtained by other techniques. The new products that will be brought to market will generally fit within these agencies' review and approval regimens.

The regulatory scheme for products is described in Chart I *Coordinated Framework—Marketing Approval of Biotechnology Products.*

CHART I.—COORDINATED FRAMEWORK—APPROVAL OF COMMERCIAL BIOTECHNOLOGY PRODUCTS

Subject	Responsible agency(ies)
Foods/Food Additives	FDA,* FSIS.[1]
Human Drugs, Medical Devices and Biologics	FDA.
Animal Drugs	FDA.
Animal Biologics	APHIS.
Other Contained Uses	EPA.
Plants and Animals	APHIS,* FSIS[1], FDA.[2]
Pesticide Microorganisms Released in the Environment All.	EPA,* APHIS.[3]
Other Uses (Microorganisms):	
Intergeneric Combination	EPA,* APHIS.[3]
Intrageneric Combination:	
Pathogenic Source Organism:	
1. Agricultural Use	APHIS.
2. Non-Agricultural use	EPA,*[4] APHIS.[3]
No Pathogenic Source Organisms	EPA Report.
Nonengineered Pathogens:	
1. Agricultural Use	APHIS.
2. Non-agricultural Use	EPA,* APHIS.[3]
Nonengineered Nonpathogens	EPA Report.

*Lead agency.
[1]FSIS, Food Safety and Inspection Service, under the Assistant Secretary of Agriculture for Marketing and Inspection Services is responsible for food use.
[2]FDA is involved when in relation to a food use.
[3]APHIS, Animal and Plant Health Inspection Service, is involved when the microorganism is plant pest, animal pathogen or regulated article requiring a permit.
[4]EPA requirements will only apply to environmental release under a "significant new use rule" that EPA intends to propose.

Jurisdiction over the varied biotechnology products is determined by their use, as has been the case for traditional products. The detailed description of the products and their review are found in the individual agency policy statements contained in this **Federal Register** Notice. The following is a brief summary of jurisdiction as described in Chart I.

Foods, food additives, human drugs, biologics and devices, and animal drugs are reviewed or licensed by the FDA. Food products prepared from domestic livestock and poultry are under the jurisdiction of the USDA's Food Safety Inspection Service (FSIS).

Animal biologics are reviewed by the Animal and Plant Health Inspection Service, (APHIS). APHIS also reviews plants, seeds, animal biologics, plant pests, animal pathogens and "regulated articles", i.e., certain genetically engineered organisms containing genetic material from a plant pest. An APHIS permit is required prior to the shipment (movement) or release into the environment of regulated articles, or the shipment of a plant pest or animal pathogen.

"Other contained uses" refers to the closed system uses of those microorganisms, subject the TSCA, that are intergeneric combinations, i.e., deliberately formed microorganisms which contain genetic material from dissimilar source organisms. These are subject to EPA's PMN requirement. EPA is considering promulgating a rule to exempt certain classes of microorganisms from this requirement.

Microbial pesticides will be reviewed by EPA, with APHIS involvement in cases where the pesticide is also a plant pest, animal pathogen, or regulated article requiring a permit. (FDA may become involved in implementing pesticide tolerances for foods.)

"Other uses (microorganisms)" include uses involving release into the environment. For these, jurisdiction depends on the characteristics of the organism as well as its use. "Intergeneric combination"* microorganisms will be reported to EPA under PMN requirements, with APHIS Involvement in cases where the microorganism is also a regulated article requiring a permit.

"Intrageneric combinations" are those microorganisms formed by genetic engineering other than intergeneric combinations. For these, when there is a pathogenic [1] source organism, and the microorganism is used for agricultural purposes, APHIS has jurisdiction. If the microorganism is used for nonagricultural purposes, then EPA has jurisdiction, with APHIS involvement in cases where the microorganism is also a

[1] "Intergeneric organisms (new organisms)" and "pathogen" are defined in section D. of the preamble.

regulated article requiring a permit. Intrageneric combinations with no pathogenic source organisms are under EPA jurisdiction although EPA will only require an informational report.

"Nonengineered pathogens" that are used for an agricultural use will fall under APHIS jurisdiction. Those that are for a nonagricultural use come under EPA jurisdiction, with APHIS involvement in cases where the microorganism is also a plant pest or animal pathogen requiring a permit. Nonengineered nonpathogenic microorganisms are under EPA jurisdiction which will require only an informational report.

Research

The coordinated framework for the regulation of biotechnology establishes requirements for the conduct of research.

Approximately ten years ago the NIH issued the NIH guidelines describing the manner in which research with organisms derived by rDNA techniques should be conducted. Since then the guidelines have been modified many times with gradual relaxation of these requirements. The guidelines prescribe the conditions under which institutions which receive NIH funds must conduct experiments. For a very small category of NIH funded experiments including environmental release, the guidelines require that the Director, NIH, approve each experiment on an individual basis. For each of these experiments, the RAC conducts a scientific review with an opportunity for public comment, and makes a recommendation to the NIH Director. As research experiments have expanded out of the biomedical area to environmental applications both agricultural and nonagricultural, other agencies have become involved, with shifting of responsibility for research approval to NSF (described in the November 85 Notice), USDA's S&E, and EPA. These other agencies' policies build, in part, on the NIH guidelines and NIH experience.

The S&E guidelines for agricultural research published separately for comment in this issue of the **Federal Register** have adopted the NIH guidelines with certain modifications including expansion of the scope to manipulation techniques other than rDNA; the table included with the S&E guidelines shows where particular elements of the NIH guidelines are used.

It should be noted that not all experiments involving the environmental release of genetically engineered organisms require prior federal approval. In plant applications there is a substantial body of research indicating that such experiments are of low risk. For certain categories of microorganisms modified by traditional genetic modification techniques, there is also a substantial body of research indicating low risk for environmental experiments.

Chart II—*Coordinated Framework—Biotechnology Research Jurisdiction* shows which agency has responsibility for a particular experiment. If more than one agency has potential jurisdiction, one agency has been designated as the lead agency and it is marked with an asterisk on Chart II. The lead agency designation depends on which research agency is funding the research (e.g., NIH, S&E, or NSF) or which regulatory agency reviews specific purpose research (e.g. pesticides). In the chart and in this discussion, the authority refers to approval of the actual execution of experiments and not to their funding.

CHART II.—COORDINATED FRAMEWORK—BIOTECHNOLOGY RESEARCH JURISDICTION

Subject	Responsible agency(ies)
Contained Research, No Release in Environment:	
1. Federally Funded	Funding agency,[1]
2. Non-Federally Funded	NIH or S&E voluntary review, APHIS.[2]
Foods/Food Additives, Human Drugs, Medical Devices, Biologics, Animal Drugs:	
1. Federally Funded	FDA*, NIH guidelines & review.
2. Non-Federally Funded	FDA*, NIH voluntary review.
Plants, Animals and Animal Biologics:	
1. Federally Funded	Funding agency,[1]* APHIS.[2]
2. Non-Federally Funded	APHIS*, S&E voluntary review.
Pesticide Microorganisms:	
Genetically Engineered:	
Intergeneric	EPA,* APHIS,[2] S&E voluntary review.
Pathogenic Intrageneric	EPA,* APHIS,[2] S&E voluntary review.
Intrageneric Nonpathogen	EPA,* S&E voluntary review.
Nonengineered:	
Nonindigenous Pathogens	EPA,* APHIS.
Indigenous Pathogens	EPA,*[3] APHIS.
Nonindigenous Nonpathogen	EPA.*
Other Uses (Microorganisms) Released in the Environment:	
Genetically Engineered:	
Intergeneric Organisms:	
1. Federally Funded	Funding agency,*[1] APHIS,[2] EPA.[4]
2. Commercially Funded	EPA, APHIS, S&E voluntary review.
Intrageneric Organisms:	
Pathogenic Source Organism:	
1. Federally Funded	Funding agency,*[1] APHIS,[2] EPA.[4]
2. Commercially Funding	APHIS,[2] EPA (* if non-agricul. USE).
Intrageneric Combination:	
No Pathogenic Source Organisms	EPA Report.
Nonengineered	EPA Report,* APHIS.[2]

* Lead Agency.

[1] Review and approval of research protocols conducted by NIH, S&E, or NSF.

[2] APHIS issues permits for the importation and domestic shipment of certain plants and animals, plant pests and animal pathogens, and for the shipment or release in the environment of regulated articles.

[3] EPA jurisdiction for research on a plot greater than 10 acres.

[4] EPA reviews federally funded environmental research only when it is for commercial purposes.

For contained federally funded research for biomedical and agricultural purposes, research approval will be granted by the funding agency. The NIH guidelines relate primarily to biomedical experiments and only to those using rDNA techniques. Research on foods/food additives, human drugs, medical devices and biologics will continue to rely on the NIH guidelines, with NIH approval required for certain experiments such as human gene therapy, and FDA permission for clinical trials.

Fashioned after the NIH guidelines, the S&E guidelines apply to agricultural research on plants, animals, and microorganisms and provide guidance for laboratory and field testing of organisms derived using rDNA manipulation and other technologies. Adherence to the appropriate set of guidelines is required for institutions receiving financial support from NIH, S&E, or NSF. These guidelines specify what type of review procedures are required for specific categories of experiments. Some experiments require individual approval by the respective agency providing institutional support. For those experiments that require agency approval, advisory committees at NIH, S&E, and NSF, composed primarily of nongovernment scientists, may be asked to provide expert review. In addition, research on plants, animals, and animal biologics will come under APHIS permit requirements if a regulated article, plant pest, animal pathogen is involved. An APHIS permit

is required prior to the shipment (movement) or release of a regulated article, or the importation or shipment of a plant pest or regulated article used in any research experiment.

EPA has authority for all environmental research on microbial pesticides regardless of whether research is federally funded or not. EPA will regulate research under a two level review system based upon its evaluation of the potential risks posed by various types of microorganisms with lesser notification required for level I reporting and full review for level II.

For the "other uses" category from Chart II (research involving nonpesticide microorganisms released into the environment), jurisdiction for release may be under S&E, NSF, APHIS, or EPA depending primarily upon the source of the funding, but also upon the purpose of the research and the characteristics of the genetically engineered microorganism. Thus, federally funded research conducted for an agricultural use will require adherence to S&E guidelines and approval of certain experiments by S&E or NIH depending on which is the funding agency. EPA will review commercial research. APHIS's jurisdiction applies to issuing permits for regulated articles, plant pests, or animal pathogens. EPA will require an informational report for nonengineered microorganisms released into the environment, with APHIS involvement for the review of plant pests or animal pathogens.

There may be situations where one agency may choose to defer to, or ask advice from, another agency. If experiments requiring NIH, NSF or S&E review/approval are submitted for review to another agency, then NIH, NSF, or S&E may determine that such review serves the same purpose, and based upon that determination, notify the submitter that no NIH, NSF, or S&E review will take place, and the experiment may proceed upon approval from the other agency.

C. Interagency Coordination Mechanisms

The Domestic Policy Council Working Group on Biotechnology

The Domestic Policy Council Working Group on Biotechnology has been responsible for this coordinated framework for the regulation of biotechnology; it also considers policy matters related to agency jurisdiction, commercialization, and international biotechnology matters. The Working Group monitors developments in biotechnology and is ready to identify problems and make appropriate recommendations for their solution. The Domestic Policy Council Working Group on Biotechnology is a continuation of a similar group established under the former Cabinet Council on Natural Resources and the Environment.

Although at the present time existing statutes seem adequate to deal with the emerging processes and products of modern biotechnology, there always can be potential problems and deficiencies in the regulatory apparatus in a fast moving field. The Working Group will be alert to the implications these changes will have on regulation, and in a timely fashion will make appropriate recommendations for administrative or legislative action.

The Biotechnology Science Coordinating Committee (BSCC)

The BSCC is responsible for coordination and consistency of scientific policy and scientific reviews. The BSCC, established October 31, 1985 as part of the Federal Coordinating Council for Science, Engineering and Technology (FCCSET), consists of senior policy officials of agencies involved in the oversight of biotechnology research and products. FCCSET is a statutory interagency coordinating mechanism managed by the Office of Science and Technology Policy, Executive Office of the President, with a mission to coordinate federal science activities among federal agencies. The November 85 Notice described the structure and activities of the BSCC.

One of the primary activities of the BSCC has been the development of definitions because a common scientific approach is essential to a coordinated federal regulatory framework. The underlying scientific issue, therefore, was defining those organisms subject to certain types of agency review.

The definitions are included in the following section of this preamble and have been incorporated, with modification, into the individual policy notices of the involved agencies. Explanatory material is also included in the agency policy statements. As mentioned elsewhere, the BSCC is seeking comments on these definitions.

Research to develop genetically modified organisms for environmental and agricultural applications (as for research on traditionally modified organisms) generally proceeds in a step-wise manner from highly contained facilities to progressively lesser degrees of containment as the investigator determines the safety and efficacy of experimental applications; these are conducted sequentially under controlled laboratory conditions, greenhouse testing, small field trials, and full field trials. The BSCC recognizes the need for further work to define the nature and extent of physical and biological barriers that limit or manage environmental release of modified organisms during greenhouse testing and field research.

The BSCC is authorized to hold public meetings in order to discuss public concerns about scientific and other issues. Accordingly, the BSCC will hold its first public meeting shortly after publication of this notice for discussion of the scientific aspects of this notice and the receipt of comments from the public. The public meeting will be held in July 1986. Details regarding time and location will be separately announced in the Federal Register.

D. BSCC Definitions

Any proposal to regulate the research and products of genetic manipulation techniques quickly confronts the issue of what organisms should be considered appropriate for certain types of review. The BSCC formulated definitions are effective immediately but are open to comment; the text following the definition of "pathogen" contains details of the request for comments.

Organisms meeting two different sets of criteria are proposed. First are organisms formed by deliberate combination of genetic material from sources in different genera. It was recognized, however, that in certain precisely constructed "intergeneric organisms" the genetic material is not considered to pose an increased risk to human health or the environment; thus, such combinations are excluded from the definition. A detailed explanation of the scientific basis for these exclusions is found in the footnote after the definition of pathogen. The BSCC specifically requests comments on whether also to consider for exclusion those organisms that exchange DNA by known physiological processes, as explained in the text immediately following the definition of "intergeneric organism (new organism)."

The second definition is "pathogen." This includes microorganisms that belong to a pathogenic species or that contain genetic material from source organisms that are pathogenic. In certain precisely constructed modified organisms, the genetic material from a pathogenic donor is not considered to pose an increased risk to human health or the environment; and, therefore, such combinations are excluded from the definition.

The BSCC definitions of "intergeneric organism (new organism)" and

"pathogen" describe the combinations genetic material that would cause a modified organism to come under review. This does not mean to suggest that the behavior of a genetically manipulated organism exempted from these definitions is wholly predictable (since any biological organism is never 100% predictable), but that the probability of any incremental hazard compared to the unmodified organism host is low. Also, this does not mean that any product manufacture or research experiment using an organism exempted from the definition should be conducted without adherence to proper manufacturing standards or research guidelines.

Given the statutory differences in the laws that they administer, the agencies adopted the principles underlying the definitions in ways consistent with their legislation. EPA, APHIS, and S&E are using the definitions to identify levels of review for microbial products within their jurisdiction. EPA, APHIS, FDA, S&E, and NSF are using the definitions as factors to consider in the review of products or experiments.

The BSCC is attempting to define what constitutes "release into the environment." The BSCC is establishing a working group on greenhouse containment and small field trials in order to develop scientific recommendations. The concept of "containment" has traditionally been used to describe physical conditions which severely limit release (for example, a contained laboratory fermentation facility). Containment can also be "biologic" because the ability of an organism to reproduce, exchange genetic information, or become established can be effectively limited biologically. Thus, the BSCC's exploration of the conditions that constitute release into the environment will consider circumstances of both physical and biological containment for particular organisms and the circumstances of their release. While the concept of physical containment may imply the high containment conditions found in certain laboratories and greenhouses, in agricultural practice many simpler effective barriers are routinely used; these include microplots for soil bacteria and fungi, paddocks for noninfective animals, and removing or covering the reproductive parts of plants and animals.

Release into the environment, for the time being, will have somewhat varying definitions for the regulatory and research review of the different agencies. There may be minor differences between agricultural and nonagricultural approaches and betweeen macro-and microorganisms.

Intergeneric Organism (New Organism)

Those organisms deliberately formed to contain an intergeneric combination of genetic material; excluded are organisms that have resulted from the addition of intergeneric materials that is well-characterized and contains only non-coding regulatory regions such as operators, promoters, origins of replication, terminators and ribosome binding regions.

"Well-characterized and contains only non-coding regulatory regions" means that the producer of the microorganism can document the following:

a. The exact nucleotide base sequence of the regulatory region and any inserted flanking nucleotides;

b. The regulatory region and any inserted flanking nucleotides do not code independently for a protein, peptide of functional RNA molecules;

c. The regulatory region solely controls the activity of other sequences that code for protein or peptide molecules or act as recognition sites for the initiation of nucleic acid or protein synthesis.

Pathogen

A pathogen is a virus or microorganism (including its viruses and plasmids, if any) that has the ability to cause disease in other living organisms (i.e., humans, animals, plants, microorganisms).

A microorganism (including viruses) will be subject to regulatory policies regarding pathogens if;

a. The microorganism belongs to a pathogenic species, according to sources identified by the agency, or from information known to the producer that the organism is a pathogen; excepted are organisms belonging to a strain used for laboratory research or commercial purposes and generally recognized as non-pathogenic according to sources identified by a federal agency, or information known to the producer and the appropriate federal agency (an example of a nonpathogenic strain of a species which contains pathogenic strains is *Escherichia coli* K–12; examples of nonpathogenic species are *Bacillus subtilis, Lactobacillus acidohilus,* and *Saccharomyces* species); or

b. The microorganism has been derived form a pathogen or has been deliberately engineered such that it contains genetic material from a pathogenic organism as defined in item a. above. Excepted are genetically engineered organisms developed by transferring a well-characterized, non-coding regulatory region from a pathogenic donor to a non-pathogenic recipient.

"Well-characterized, non-coding regulatory region" means that the producer of the microorganism can document the following:

a. The exact nucleotide base sequence of the regulatory region and any inserted flanking nucleotides;

b. The regulatory region and any inserted flanking nucleotides do not code independently for a protein, peptide, or functional RNA molecules; and,

c. The regulatory region solely controls the activity of other sequences that code for protein or peptide moldecules or act as recognition sites for the initiation of nucleic acid or protein systhesis.

This definition excludes organisms such as competitors or colonizers of the same substrates, commensal or mutualistic microorganisms, or opportunistic pathogens.

The footnote contains the scientific basis for exempting non-coding regulatory regions from the definitions of intergeneric organisms and pathogen.[2]

[2] The BSCC has based the exemption of intergeneric transfers of regulatory regions on their lack of coding capacity for the production of proteins, peptides or functional RNA molecules. It has been recommended by other members of the scientific community that there should be additional exemptions such as ribosomal proteins, ribosomal RNAs and transfer RNAs. The BSCC has chosen to examine these suggestions in more detail during the next few months. At the present the BSCC has excluded:

1. Origins of replications;
2. Ribosome binding sites;
3. Promoters;
4. Operators; and,
5. Terminators.

The basis for these exemptions is as follows. Each of these regulatory elements has no coding capacity for the production of any gene product and therefore does not promote the production of any new material. What these elements are responsible for is the initiation and modulation of nucleic acid synthesis at the specific region where they appear in the chromosome.

Bacterial genes are precisely regulated and this regulation is based on a series of regulatory elements. The principal regulatory unit is the *operon.* Operons are controlled primarily, but not exclusively, through the regulation of the rate of initiation of messenger RNA synthesis. This regulation is based on the interaction of two short nucleotide sequences in the DNA, the *promoter,* which is the site of RNA polymerase binding and the *operator,* which follows closely and acts as an off-on switch for the movement of the polymerase into the structural gene which follows. The function of the operator is to *bind* a cellular repressor protein which is synthesized in response to changing nutritional stimuli. *Terminator* regions are short nucleotide sequences which signal the termination of mRNA synthesis by the polymerase. They act as a signal for the dissociation of the polymerase from the DNA.

Replication of DNA in every biological system that has been examined is initiated at a specific site or group of sites in the chromosome. Those sites have broad specificity and a DNA molecule without the appropriate site will not be replicated. The sites which are critical to the initiation of replication are known as *origins of replication.* These regions are short nucleotide sequences which serve as initiation sites for specific enzyme action during the DNA replication process. For example, in order for mammalian DNA to replicate in bacteria, it must be associated with a bacterial origin of replication and vice versa.

Ribosome binding sites are short nucleotide segments at the beginning of messenger RNA molecules which signal the attachment of ribosomes for the initiation of protein synthesis. Functioning in this role they are not translated into the protein or peptide being processed.

The BSCC is requesting comments on these definitions during the period of sixty days following the date of this notice and specifically seeks comments addressing the following:

1. The suitability and applicability of these definitions to applications involving release into the environment, contained industrial large-scale applications, foods/food additives, drugs, medical devices, and other possible products.

2. Whether combinations of genetic material from organisms that exchange DNA by known physiological processes should be excluded from the definition of intergeneric organisms: i.e., should organisms be excluded which contain intergeneric combinations of certain specified rDNA molecules that consist entirely of DNA segments from different genera that exchange DNA by known physiological processes? As certain rDNA organisms are exempted under section III–D–4 of the NIH guidelines, the question was raised whether these organisms when used in the environment should be similarly exempted from federal product review. This exemption would not, however, exclude from review such "natural exchangers" that are also pathogens or plant pests. In the event that the exclusion of such different species that exchange DNA by known physiological processes is accepted as appropriate, a list of such species combinations that has been maintained and updated by the Office of Recombinant DNA Activities of the National Institutes of Health will be updated, in light of environmental use.

3. What are the most appropriate definitions of "release into the environment" for macro- and microorganisms.

E. International Aspects

The United States seeks to promote international scientific cooperation and understanding of scientific considerations in biotechnology on a range of technical matters. These activities add to scientific knowledge and ultimately contribute to protection of health and the environment.

The United States also seeks to reduce barriers to international trade. U.S. agencies apply the same regulation and approval procedures on domestic and foreign biotechnological products. We are seeking recognition among nations of the need to harmonize, to the maximum extent possible, national regulatory oversight activities concerning biotechnology. Barriers to trade in biotechnological products should be avoided as nations join together in working toward this mutual goal.

The U.S. agencies that have published separate policy statements as part of this notice are committed to the policy described in this section on international harmonization and have incorporated by reference the language in this International Aspects section as part of their respective agency policy statements.

Organization for Economic Cooperation and Development (OECD)

The approach of the comprehensive framework contained in this notice takes into account, *inter alia*, the broad goals described by an Ad Hoc Group of Government Experts convened by OECD in their recent report entitled, *"Recombinant DNA Safety Considerations, Safety Considerations for Industrial, Agricultural and Environmental Applications of Organisms Derived by Recombinant DNA Techniques."* The United States is pleased to have had the opportunity for its experts to work with those of other governments in the preparation of this report. The report includes the following concepts:

Summary of Major Points

Recombinant DNA techniques have opened up new and promising possibilities in a wide range of applications and can be expected to bring considerable benefits to mankind. They contribute in several ways to the improvement of human health and the extent of this contribution is expected to increase significantly in the near future.

The vast majority of industrial rDNA large-scale applications will use organisms of intrinsically low risk which warrant only minimal containment, Good Industrial Large-Scale Practice (GILSP).

When it is necessary to use rDNA organisms of higher risk, additional criteria for risk assessment can be identified and furthermore, the technology of physical containment is well known to industry and has successfully been used to contain pathogenic organisms for years. Therefore, rDNA microorganisms of higher risks can also be handled safely under appropriate physical and/or biological containment.

Assessment of potential risks of organisms for environmental or agricultural applications is less developed than the assessment of potential risks for industrial applications. However, the means for assessing rDNA organisms can be approached by analogy with the existing data base gained from the extensive use of traditionally modified organisms in agriculture and the environment generally. With step-by-step assessment during the research and development process, the potential risk to the environment of the applications of rDNA organisms should be minimized.

I. General Recommendations

1. Harmonization of approaches to rDNA technology can be facilitated by exchanging: Principles or guidelines for national regulations; developments in risk analysis; and practical experience in risk management. Therefore, information should be shared as freely as possible.

2. There is no scientific basis for specific legislation for the implementation of rDNA technology and applications. Member countries should examine their existing oversight and review mechanisms to ensure that adequate review and control may be applied while avoiding any undue burdens that may hamper technological developments in this field.

3. Any approach to implementing guidelines should not impede future developments in rDNA technology. International harmonization should recognize this need.

4. To facilitate data exchange and minimize trade barriers between countries, further developments such as testing methods, equipment design, and knowledge of microbial taxonomy should be considered by both national and international levels. Due account should be taken of ongoing work on standards within international organizations such as: World Health Organization; Commission of the European Communities; International Standards Organization; Food and Agricultural Organization; and, Microbial Strains Data Network.

5. Special efforts should be made to improve public understanding of various aspects of rDNA technology.

6. For rDNA applications in industry, agriculture and the environment, it will be important for OECD Member countries to watch the development of these techniques. For certain industrial applications and for environmental and agricultural applications of rDNA organisms, some countries may wish to have a notification scheme.

7. Recognizing the need for innovation, it is important to consider appropriate means to protect intellectual property and confidentiality interests while assuring safety.

II. Recommendations Specific for Industry

1. The large-scale industrial application of rDNA technology should wherever possible utilize microorganisms that are intrinsically of low risk. Such microorganisms can be handled under conditions of Good Industrial Large-Scale Practice (GILSP).

2. If, following assessment using the criteria outlined in the document, a rDNA microorganism cannot be handled merely by GILSP, measures of containment corresponding to the risk assessment should be used in addition to GILSP.

3. Further research to improve techniques for monitoring and controlling non-intentional release of rDNA organisms should be encouraged in large-scale industrial applications requiring physical containment.

III. Recommendations Specific for Environmental and Agricultural Applications

1. Considerable data on the environmental and human health effects of living organisms

exist and should be used to guide risk assessments.

2. It is important to evaluate rDNA modified organisms for potential risk, prior to applications in agricultural and the environment. However, the development of general international guidelines governing such applications is premature at this time. An independent review of potential risks should be conducted on a case-by-case basis prior to application. Case-by-case means an individual review of a proposal against assessment criteria which are relevant to the particular proposal; this is not intended to imply that every case will require review by a national or other authority since various classes of proposals may be excluded.

3. Development of organisms for agricultural or environmental applications should be conducted in a stepwise fashion, moving, where appropriate, from the laboratory to the growth chamber and greenhouse, to limited field testing and finally, to large-scale field testing.

4. Further research to improve the prediction, evaluation, and monitoring of the outcome of applications of rDNA organisms should be encouraged.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 84N-0431]

Statement of Policy for Regulating Biotechnology Products

AGENCY: Food and Drug Administration.

ACTION: Final policy statement for regulating biotechnology products.

SUMMARY: In the **Federal Register** of December 31, 1984 (43 FR 50878), the Food and Drug Administration (FDA) published a policy statement for regulating biotechnology products. The policy statement was part of a larger document that included an index of U.S. laws related to biotechnology, a description of the policies of the major regulatory agencies that are involved in reviewing the products of biotechnology, a description of a proposed scientific advisory mechanism for assessment of biotechnology issues, and an explanation of how the activities of the Federal agencies involving biotechnology will be coordinated. Of the comments FDA received on the policy statement, most favored the policy statement; some requested further clarification and guidance. The current action constitutes FDA's final policy statement which has been revised in response to the comments.

ADDRESS: Written comments should be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Dr. Mary Ann Danello (HF-5), Food and Drug Administration, Room 14-90, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4650.

SUPPLEMENTARY INFORMATION: FDA's policy statement of December 31, 1984 stated the FDA regulation must be based on the rational and scientific evaluation of products, and not on *a priori* assumptions about certain processes. Accordingly, FDA's administrative review of products, including those that employ specialized biotechnological techniques, is conducted in the light of the intended use of a product on a case-by-case basis. FDA believes the agency need not establish new administrative procedures to deal with generic concerns about biotechnology.

These views were supported by the majority of comments received in response to FDA's notice. Thirty-four comments were received, with 12 from manufacturers of regulated products, 16 from associations and universities, and 6 from individuals. A summary of the comments and the agency's response to them follow:

1. Many commenters urged the agency to publish additional "Points to Consider" documents to provide further guidance for biotechnology product applicants. These commenters specifically requested guidance in the area of animal drugs (especially protein drugs) and human foods and food additives.

FDA agrees that "Points to Consider" documents provide useful guidance, especially in areas involving new biotechnology, and will consider developing these documents where appropriate.

2. Related comments raised questions on FDA's general requirements for approving biotechnology products that are animal drugs, human foods, or food additives.

In response to these comments, FDA has amended the animal drug section ("General Requirements for Animal Food Additives and Drugs") to be more informative and has added a new section concerning its policies on human foods and food additives (see "General Requirements for Human Foods and Food Additives").

3. Many comments questioned the need for new or supplemental marketing applications for biotechnology products that are identical to products derived from conventional technology.

The agency has re-examined this issue and continues to believe that, as a general principle, new marketing applications will be required for most products manufactured using new biotechnology. For example, use of recombinant DNA (rDNA) technology has the potential to lead to new structural features in the product, result in product micro-heterogeneity, or introduce new contaminants (e.g., associated with new cell substrates), each of which may affect the safety, efficacy and stability of the product. Because of potential differences in the products resulting from use of recombinant DNA technology, the resulting products may be "new" products requiring separate approval under the applicable statutory provisions. However, each case will be examined separately to determine the appropriate information to be submitted. In some instances complete new applications may not be required. For example, the sponsor of a conventionally produced animal drug product who manufactures an identical or virtually identical product using biotechnology may be required to submit only a supplemental application. However, if the animal drug product manufactured using biotechnology differs significantly from the product manufactured by conventional processes, a complete original application would be required. The agency believes that each product must undergo adequate and appropriate testing and review to ensure that it is safe and effective regardless of the technology employed. Sponsors are urged to communicate with FDA to establish the scope of information required for products of biotechnology.

4. Many comments questioned the need for the proposed review mechanism by a Biotechnology Science Board (BSB). These comments stated that the additional layer of review would cause delays in the product approval process.

A notice published in the **Federal Register** of November 14, 1985 (50 FR 47174) discussed the establishment of the Biotechnology Science Coordinating Committee (BSCC) within the Federal Coordinating Council for Science, Engineering and Technology. That notice addressed various criticisms of the BSB. FDA believes that the new BSCC will facilitate sharing of biotechnology information among agencies and will not delay agency reviews of product applications.

In view of the foregoing, FDA's final policy statement for regulating biotechnology products reads as follows:

Introduction

A small but important and expanding fraction of the products the Food and Drug Administration (FDA) regulates represents the fruits of new technological achievements. These achievements are in areas as diverse as polymer chemistry, molecular biology, and micro-miniaturization. It is also noteworthy that technological advancement in a given area may give rise to very diverse product classes, some or all of which may be under FDA's regulatory jurisdiction. For example, new developments in recombinant DNA research can yield products as diverse as food additives, drugs, biologics, and medical devices.

Although there are no statutory provisions or regulations that address biotechnology specifically, the laws and regulations under which the agency approves products place the burden of proof of safety as well as effectiveness of products on the manufacturer. The agency possesses extensive experience with these regulatory mechanisms and applies them to the products of biotechnological processes. In this notice, FDA proposes no new procedures or requirements for regulated industry or individuals. Rather, the administrative review of products using biotechnology is based on the intended use of each product on a case-by-case basis.

The marketing of new drugs and biologics [1] for human use, and new animal drugs, requires prior approval of an appropriate new drug application (NDA), biological product license, or new animal drug application (NADA). For new medical devices, including diagnostic devices for human use, either a premarket approval application (PMA) or reclassification petition is required. If the device is determined to be substantially equivalent to an already marketed device, a premarket notification under section 510(k) of the Federal Food, Drug, and Cosmetic Act (the act) is required. For food products, section 409 of the act requires preclearance of food additives including those prepared using biotechnology. Section 706 of the act requires preclearance of color additives. The implementing regulations for food and color additive petitions and for affirming generally recognized as safe (GRAS) food substances are sufficiently comprehensive to apply to those involving new biotechnology.

Genetic manipulations of plants or animals may enter FDA's jurisdiction in other ways; for example, the introduction into a plant of a gene coding for a pesticide or growth factor may constitute adulteration of foodstuff derived from the plant, or the use of a new microorganism found in a food such as yogurt could be considered a food additive. Such situations will be evaluated case-by-case and in cooperation with the U.S. Department of Agriculture (USDA), where appropriate.

The Regulatory Process

Congress has provided FDA authority under the act and the Public Health Service (PHS) Act to regulate products regardless of how they are manufactured. Each request for product approval will be considered using the appropriate statutory and regulatory criteria. The following sections summarize general requirements for various kinds of products and address specific comments concerning particular product categories. Individual regulations should be consulted for additional details.

General Requirements for New Drugs and Biologics for Human Use

A new drug is, in general terms, a drug not generally recognized by qualified scientific experts as safe and effective for the proposed use. New drugs may not be marketed unless they have been approved as safe and effective for their intended uses. Clinical investigations on human subjects by qualified experts are a prerequisite for the determination of safety and effectiveness. Sponsors of investigations of new drugs or new uses of approved drugs file a Notice of Claimed Investigational Exemption for a New Drug (IND) to conduct clinical investigations on human subjects. The IND must contain information to demonstrate the safety of proceeding to test the drug in human subjects, including, for example, drug composition, manufacturing and controls data, results of animal testing, training and experience of investigators, and a plan for clinical investigation. In addition, assurance of informed consent and protection of the rights and safety of human subjects is required. FDA evaluates IND submissions and reviews ongoing clinical investigations. Significant changes in the conditions of the study, including changes in study design, drug manufacture or formulation, or proposals for additional studies, must be submitted to FDA as amendments to the IND.

FDA approval of an NDA or an abbreviated New Drug Application (ANDA) is required before the new drug can be marketed. The NDA must contain, among other information, the following:

- A list of components of the drug and a statement of the composition of the drug product;
- A description of the manufacturing and packaging procedures and controls for the drug product;
- A description of the nonclinical studies concerning the drug's pharmacological actions and toxicological effects;
- A description and analysis of each clinical study; and
- A description and analysis of any other data or information relevant to an evaluation of the safety and effectiveness of the drug product, including commercial marketing experience.

NDA holders who intend to market an approved drug under conditions other than those approved in the NDA must submit a supplemental NDA containing clinical evidence of the drug's safety and effectiveness for the added indications. Extensive changes such as a change in formula, manufacturing process, or method of testing differing from the conditions of approval outlined in the NDA may also require additional clinical testing.

Biological products must also be approved by FDA prior to marketing, as required by section 351 of the PHS Act. A biological product is "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product * * * applicable to the prevention, treatment, or cure of diseases or injuries of man * * *." Unapproved biological products are regulated under the same regulations as new drugs during the IND phase. Prior to marketing, separate licenses are issued for the manufacturing establishment and the biological product. The manufacturing establishment and the biological product must meet standards (including any FDA standards specific for the product) designed to ensure the safety, purity, potency, and efficacy of the product. To obtain a license, the facility must also pass a prelicensing inspection. Licensed products are subject to specific requirements for lot release of FDA.

Manufacturers of new drugs and biologics must operate in conformance with current good manufacturing practice (CGMP) regulations. These

[1] FDA endorses the BSCC definitions of "intergeneric" (new) organism or "pathogen" found in the preamble, believing that they describe the microorganisms appropriate for review when environmental or agricultural applications of the microorganisms are contemplated (and see pp. 22–25). As discussed below in this notice, "new" drugs, biologics, medical devices, and food additives are defined in the statutes establishing FDA's jurisdiction over such products.

regulations require adequately equipped manufacturing facilities, adequately trained personnel, stringent control over the manufacturing process, and appropriate finished product examination. CGMP's are designed to protect the integrity and purity of the product.

The sponsor's process techniques are also considered in FDA's reviews and communications for the development of appropriate information on which the submission of an NDA, ANDA, or biological product license application would be based. For example, the use of recombinant DNA technology to manufacture new drugs or biological products may result in products that differ from similar products manufactured with conventional methods. Determination of the extent of testing required will depend upon the nature of the particular product. In some instances the molecular structure of the product may differ from the structure of the active molecule in nature. For example, the first human growth hormone manufactured using recombinant microorganisms has an extra amino acid, an amino-terminal methionine; hence, it is an analogue of the native hormone. Such differences could affect the drugs's activity or immunogenicity and, consequently, could affect the extent of testing required.

Another consideration in the review of new drugs or biological products producted by recombinant techniques is whether the manufacturing process includes adequate quality controls. For example, the occurrence of mutations in the coding sequence of the cloned gene during fermentation could give rise to a subpopulation of molecules with an anomalous primary structure and altered activity. This is a potential problem inherent in the production of polypeptides in any fermentation process. As with conventionally produced products, assurance of adequate processing techniques and controls is important in the manufacturing of any biotechnology-produced new drug or biological product. Review of the production of human viral vaccines routinely involves a number of considerations including the purity of the media and the serum used to grow the cell substrate, the nature of the cell substrate, and the characterization of the virus. In the case of live viral vaccine, the final product is biologically active and is intended to replicate in the recipient. Therefore, the composition, concentration, subtype, immunogenicity, reactivity, and nonpathogenicity of the vaccine preparation are all considerations in the final review, whatever the techniques employed in "engineering" the virus. However, special considerations may arise based upon the specific technology employed. For example, a hepatitis B vaccine produced in yeast (via recombinant DNA techniques) would be monitored for yeast cell contaminants, while distinctly different contaminants would be of concern in a similar vaccine produced from the plasma of infected patients.

Nucleic acids or viruses used for human gene therapy will be subject to the same requirements as other biological drugs. It is possible that scientific reviews of these products will also be performed by the National Institutes of Health.

To provide guidance to current or prospective manufacturers of drugs and biological products, the FDA has developed a series of documents describing points that manufacturers might wish to consider in the production and testing of products. The "Points to Consider" documents generated to date include several topics: interferon, monoclonal antibodies, products of recombinant DNA technology, and the use of new cell substrates. These "Points to Consider" documents are available from the agency upon request from the Office of Biological Investigational New Drugs (301–443–4864). FDA plans to develop additional "Points to Consider" in areas of scientific interest to manufacturers of new drugs and biologics.

General Requirements for Animal Food Additives and Drugs

Animal food additives and drugs are subject to similar mandatory requirements of the act as the like products for use in humans. Animal biologics, however, are licensed by the U.S. Department of Agriculture (USDA) under the authority of the Virus-Serum-Toxin Act of 1913. Questions as to whether a product is an animal biological subject to USDA licensure, or a new animal drug to be regulated by FDA are referred to a standing committee of representatives from USDA and FDA.

New animal drugs must go through the Investigational New animal Drug (INAD) and New Animal Drug Application (NADA) process, a procedure similar to that required for human drugs, as discussed earlier. However, INAD regulations do not require advance agency approval for clinical investigations for the drug, although authorization is required for use of edible products derived from food-producing animals in which the drug has been used. The data must be specific for each animal species for which the drug is intended. For NADA approval, it must be shown that the product is safe and effective when used in accordance with approved label directions. Also, it must be shown that those drugs which are intended for use in food-producing animals and used in accordance with approved label directions, do not accumulate as unsafe residues in the edible tissues of the animal at the time of slaughter. Moreover, the manufacturer must submit acceptable methods for measurement of any drug residue in edible tissues. Further, animal drugs, including premixes for use in medicated feeds and medicated feeds, must be manufactured in conformance with CGMPs. Substances that are used in animal feeds, other than drugs, and that are produced by recombinant DNA technology, are considered to be food additives and require approval of a separate food additive petition (FAP), even though a similar substance is currently approved as a food additive.

There have been questions about the requirement of an orginal application for a biotechnology product, even when the product is identical to a currently approved animal drug held by the same applicant. FDA's Center for Veterinary Medicine (CVM) has determined that, when the new substance produced by biotechnology is identical or virtually identical to an approved substance produced by conventional technology, only a supplemental application is necessary. Of course, in this instance the sponsor of the biotechnology product must also be the sponsor of the conventionally produced product. If, on the other hand, the new substance produced by biotechnology is significantly different from that produced by conventional means, an original application will be needed.

Two examples, each involving the adoption of rDNA technology as an alternative means of producing a substance that is currently the subject of an approved NADA, will illustrate. In the first example, the drug is (or appears to be) unchanged by the new production method. Under the current regulations, such a departure in manufacturing procedure requires a supplemental application which requires approval before implementation. The supplement would be a Category II supplement under CVM's supplemental policy in that it involves a revised method of synthesis or fermentation for the new drug substance. However, in accordance with the CVM's supplemental policy the underlying safety and effectiveness data

supporting the original NADA usually would not be reviewed (for compliance with contemporary standards) since there is likely no increased risk of human exposure to the drug. Data may be required to demonstrate the new animal drug product is essentially biologically equivalent to the drug product for which approval has already been granted. Approval of such a supplemental NADA is not required to be published in the **Federal Register.**

In the second example, a new method of manufacture changes the molecular structure or chemcial composition of the active ingredient. Such a change in the identity of the new animal drug normally will require an original new animal drug application and subsequent publication of a notice of approval in the **Federal Register.** Ordinarily, an original NADA requires complete safety and effectiveness studies, meeting contemporary standards. However, reference to data in another NADA sometimes suffices to support a separate NADA approval, where the existing NADA is owned by the applicant of the new NADA, or where the new applicant obtains authorization to refer to another NADA. In this case, reference might be made to data contained in the NADA supporting approval of the drug as produced by conventional means.

It may be possible to regard the new application as if it were a Category II supplement. This finding would be dependent upon data showing the new substance to be sufficiently similar to the original in terms of its pharmacology, toxicology, bioequivalence, and metabolism.

Thus, regardless of the type of application required, there is no legal requirement for the generation of new safety and effectiveness data if the applicant has access to previously submitted data, and there is no scientific need.

General Requirements for Medical Devices

Medical devices for human use are regulated by requirements of the act as amended by the Medical Device Amendments of 1976. In general, a device is a health care product that does not achieve any of its principal intended purposes by chemical action in or on the body or by being metabolized. Devices include diagnostic aids such as reagents, antibiotic sensitivity discs, and test kits for *in vitro* diagnosis of disease.

The act establishes three classes of devices: Class I (general controls), class II (performance standards), and class III (premarket approval). Classification of a device is determined by the level of regulatory control needed to provide reasonable assurance of the safety and effectiveness of the device. A class I device is a device for which the "general controls" authorized by or under various sections of the act are sufficient to provide reasonable assurance of the safety and effectiveness of a device. A class II device is a device for which general controls by themselves are insufficient to provide reasonable assurance of the Safety and effectiveness of the device, for which there is sufficient information to establish a performance standard to provide such assurance, and for which it is therefore necessary to establish a performance standard to provide reasonable assurance of its safety and effectiveness. A class III device is a device that cannot be classified into class I or class II and that is purported or represented to be for use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human, health, or that presents a potential unreasonable risk of illness or injury. Premarket approval obtained in accordance with section 515 of the act is required to provide reasonable assurance of the safety and effectiveness of a class III device.

Before a manufacturer may introduce into commerce any medical device it has not previously marketed, the manufacturer must submit to FDA a premarket notification. This notification requirement is designed to assure that manufacturers do not intentionally or unintentionally circumvent the automatic classification into class III of devices not on the market prior to enactment of the Medical Device Amendments and not substantially equivalent to pre-amendment devices.

A new device, that, is one not substantially equivalent to a pre-amendments device, remains a class III device requiring FDA approval of a premarket approval application (PMA) unless FDA reclassifies it into class I or class II, usually in response to a manufacturer's petition. In the premarket approval process the manufacturer must establish by valid scientific evidence that the device is safe and effective for its intended use. This evidence usually is data from clinical investigations.

For a significant risk device, as defined in FDA's regulations, the sponsor must submit an application to FDA for approval to conduct a clinical investigation. This application seeks an Investigational Device Exemption. When the manufacturer believes that there are sufficient data to establish the safety and effectiveness of its device, the manufacuter files a PMA.

General Requirements for Foods

Several sections of the Food, Drug and Cosmetic Act apply to the Agency's regulation of food. No particular statutory provision or regulation deals expressly with food produced by new biotechnology. Accordingly, when confronted by an issue concerning the regulation of food produced by new biotechnology, the Agency will apply the relevant statutory or regulatory provisions. Most issues concerning the safety of a food will involve the application of either section 402(a)(1) or section 409 of the Act.

Section 402(a)(1) of the Act provides, in part, that a food is adulterated if it bears or contains any poisonous or deleterious "added substance" which may render it injurious to health." Courts have agreed with the agency's interpretation of this section that any substance that is not an inherent constituent of food may be regulated as an "added substance." *See*, for example, *United States* v. *Cartons of Swordfish*, 395 F. Supp. 1194 (S.D.N.Y. 1975). Furthermore, if the quantity of the constituent exceeds the amount that would normally be present because of some technological adjustment to the product, that excess quantity may also be viewed as "added substance" within the meaning of the section. *See United States* v. *Anderson Sea Foods, Inc.*, 622 F.2d 157 (5th cir. 1980). Thus, section 401(a)(1) applies to most of the harmful substances that may occur in human food. For example, is a food produced by new biotechnology contains a higher level of a substance than it might ordinarily have, then that level "may be injurious to health" and the agency could regulate the product under section 402(a)(1). Similarly, if a food produced by new biotechnology contains, as a result of the production process, a harmful or deleterious substances not contained ordinarily in the food, the food could be in violation of the section.

The other primary statutory provisoins that FDA relies upon in determining the safety of food and food constituents are sections 201(s) and 409, the food additive provisions of the Act. The definition of food additive appears in section 201(s) of the Act and includes both artificial and natural substances. The definition provides that:

> the term food additive means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including

any source of radiation intended for any such use), if such substance is not generally recognized as safe by qualified experts.

If the substance is generally recognized as safe (GRAS) for a given food use, the product is not a food additive.

Comments questioned whether a substance (including microbes) that is GRAS could lose its GRAS status solely because it was produced or modified by new biotechnology. The answer is yes, if the substance (and its contaminants) has been altered in such a way that it can no longer be generally recognized by qualifed experts to be safe. In this instance, the substance would be a food additive and the provisions of section 409 would apply. Section 409 provides that in order to be lawfully used in food, a food additive must be the subject of an approved food additive regulation, published upon approval of a food additive petition. The FDA may not approve a food additive regulation until certain basic evidentiary criteria are met. Most important of these is that the additive must be shown to be safe under the conditions that it will be used. This requires a demonstration to a reasonable certainty that the additive will not adversely affect the health of consumers.

FDA anticipates that the techniques of new biotechnology used in producing food will, for the most part, involve rDNA and microbial isolation. The agency applies certain general principles that it will follow in determining the safety of foods produced by such techniques.

When determining the safety of food produced by rDNA techniques, the agency takes into consideration, but is not restricted to, whether:

1. The cloned DNA as well as the vector used are properly identified;
2. The details of the construction of the production organism are available;
3. There is information documenting that the inserted DNA is well-characterized [2] and free from sequences that code for harmful products, and
4. The food produced is purified, characterized, and standardized.

When determining the safety of food produced by microbial isolation, the agency will take into consideration, but is not restricted to, whether:

1. The microbial isolate used for production is identified taxonomically, and if the strain of the isolate has been genetically manipulated, whether each strain contributing genetic information to the production strain is identified;
2. The cultural purity and genetic stability of isolate has been maintained;
3. Fermentation has been performed with a pure culture and monitored for purity;
4. The microbial isolate used for production also produces antibiotics or toxins;
5. The isolates are pathogenic;[3] and
6. Viable cells of the production strain are present in the final product.

As a general rule, the extent of testing required on a food product produced by biotechnology will depend upon many factors, including the novelty of the substances used to produce the food (e.g., whether a substance is an "intergeneric" organism, as defined by the BSCC definitions in the preamble), the purity of the resulting product, and the estimated consumption of the product.

The agency will require that the final product intended for commercialization be the article tested. A complete discussion of FDA's toxicology requirements is found in the FDA publication, "Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food." This publication is available through the National Technical Information Service (publication # PB 83-170696) 5285 Port Royal Road, Springfield, VA 22161. Questions concerning the publication can be directed to Dr. Alan M. Rulis in the Center for Food Safety and Applied Nutrition (CFSAN) at (301) 472-5676.

Obligations Under the National Environmental Policy Act

All premarketing approvals of FDA-regulated products are subject to the requirements of the National Environmental Policy Act (NEPA) as defined by the Council on Environmental Quality's regulations (40 CFR Parts 1500-1508) and as further described by FDA's NEPA-implementing procedures (21 CFR Part 25, final rule published April 26, 1985; 50 FR 16636). For new products or major new uses for existing products, these procedures ordinarily require the preparation of an environmental assessment. An environmental impact statement is required if the manufacture, use, or disposal of the product is anticipated to cause significant environmental impacts.

International Aspects

FDA is committed to the policy described in the section entitled "International Aspects" in the Office of Science and Technology Policy General Preamble, published in today's **Federal Register.**

ENVIRONMENTAL PROTECTION AGENCY

[OPTS-00049A]

Statement of Policy; Microbial Products Subject to the Federal Insecticide, Fungicide, and Rodenticide Act and the Toxic Substances Control Act

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: This notice describes how EPA is addressing certain microbial products of biotechnology under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA). The notice outlines EPA's plan for review of microbial pesticides under FIFRA with particular emphasis on small-scale field testing of genetically engineered, nonindigenous, and pathogenic microbial pesticides. It also announces EPA's policy for addressing new microbial products that fall under TSCA authority. This includes EPA's interpretation of the new chemical premanufacture notification (PMN)

[2] As defined by the BSCC definitions in the preamble, "well-characterized" means that the producer can document the exact nucleotide sequence of the insert and any flanking nucleotides.

[3] A pathogen is a virus or microoganism (including its viruses and plasmids, if any) that has the ability to cause disease in other living organisms (i.e., humans, animals, plants, microorganisms).

A microorganism will be included within this definition if:

a. The microorganism belongs to a pathogenic species, according to sources identified by the agency, or from information known to the producer that the organism is a pathogen; excepted are organisms belonging to a strain used for laboratory research or commercial purposes and generally recognized as nonpathogenic according to sources identified by a federal agency, or information known to the producer and the appropriate federal agency; an example of a nonpathogenic strain of species which contains a pathogenic strain is Escherichia coli K-12; examples of nonpathogenic species are Bacillus subtilis, Lactobacillus acidophilus, and Saccharomyces species; or

b. The microorganism has been derived from a pathogen or has been deliberately engineered such that it contains genetic material from a pathogenic organism as defined in item a. above. Excepted are genetically engineered organisms developed by transferring a well-characterized, non-coding regulatory region from a pathogenic donor to a non-pathogenic recipient.

"Well-characterized, non-coding regulatory region" means that the producer of the microorganism can document the following:

a. The exact nucleotide base sequence of the regulatory region and any inserted flanking nucleotides;

b. The regulatory region and any inserted flanking nucleotides do not code independently for protein, peptide, or functional RNA molecules; and,

c. The regulatory region solely controls the activity of other sequences that code for protein or peptide molecules or act as recognition sites for the initiation of nucleic acid or protein synthesis.

This definition excludes organisms such as competitors or colonizers of the same substrates, commensal or mutualistic microorganisms, or opportunistic pathogens.

provisions of TSCA section 5 for new genetically engineered microorganisms used for commercial purposes, and the Agency's intentions to develop, under TSCA, a significant new use rule for pathogenic microorganisms; a rule modifying the PMN research and development exemption so that small scale field testing of microorganisms for TSCA purposes is subject to PMN; a section 8(a) reporting rule for other microorganisms prior to their release in the environment; and section 5(h)(4) exemptions as appropriate.

DATES: The following policies and requirements announced in this notice are effective June 26, 1986: (1) The notification and reporting requirements for small-scale field tests and the experimental use permit and registration requirements for microbial pesticides under FIFRA, described in Unit II.D of this notice; (2) premanufacture notice requirements under TSCA for "new" microorganisms, as defined in Unit III.C.1 and Unit IV of this notice, except those produced only in small quantities solely for research and development; (3) TSCA section 8(e) reporting requirements for information on substantial risks posed by microorganisms subject to TSCA, as described in Unit III.C.5 of this notice; and (4) FIFRA section 6(a)(2) reporting requirements for information on unreasonable adverse effects posed by microbial pesticides. EPA requests that persons voluntarily comply with other policies announced in this notice, as summarized in Unit I.C, until rules implementing them are promulgated.

ADDRESS: Comments on this EPA notice should be identified by Docket Number OPTS-00049A and addressed to: Document Control Officer (TS-790), Office of Toxic Substances, Environmental Protection Agency, Rm. E-201, 401 M. St. SW., Washington, DC 20460.

Information submitted as comments on this EPA notice may be claimed confidential by marking any part or all of that information as "Confidential Business Information." Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR Part 2. A sanitized copy of any material containing Confidential Business Information must be provided by the submitter for inclusion in the public record. Information not marked confidential may be disclosed publicly by EPA without prior notice.

Comments received on this notice, except those containing Confidential Business Information, will be available for review and copying from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays, in the TSCA Public Information Office, Rm. E-107 at the address given above.

FOR FURTHER INFORMATION CONTACT:

For general information including copies of this EPA notice and related materials: Edward A. Klein, Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Environmental Protection Agency, Rm. E-543, 401 M St., SW., Washington, DC 20460,Toll-free: (800-424-9065), in Washington, DC: (202-554-1404), outside the USA: (Operator 202-554-1404).

For technical information regarding the FIFRA section of the EPA policy:

By mail: Frederick S. Betz, Hazard Evaluation Division (TS-769C), Office of Pesticide Programs, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460.

Office location and telephone number: Rm. 1128, Crystal Mall #2, 1921 Jefferson Davis Highway, Arlington, VA (703-557-9307).

For technical information regarding the TSCA sections of the EPA policy: Anne K. Hollander, Office of Toxic Substances (TS-794), Environmental Protection Agency, Rm. E-511, 401 M St., SW., Washington, DC 20460 (202-382-3852).

SUPPLEMENTARY INFORMATION:

Table of Contents

Following is a table of contents for the EPA portion of this notice:

I. Overview

A. Purpose

For centuries, humans have used organisms to generate commercial products or to perform useful functions. During the last decade, advances in the biological sciences have increased the ability of humans to change or combine the inherited characteristics of microorganisms, plants, and animals. These advances, along with more traditional genetic engineering and biological techniques, are expected to lead to a wide variety of useful products. Among these are microorganisms that will be used to degrade toxic pollutants, leach minerals, enhance oil recovery, produce industrial chemicals, and act as pesticides. As with chemicals used for the same types of purposes, many of these microorganisms will be reviewed by EPA for potential health and environmental risks.

Specifically, EPA reviews and may register pesticide products under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and reviews chemical substances (except those used as pesticides, foods, food additives,

cosmetics, drugs, and medical devices) under the Toxic Substances Control Act (TSCA). EPA's Office of Pesticides and Toxic Substances (OPTS) is responsible for implementing both FIFRA and TSCA.

This notice describes how EPA plans to address microbial products that are subject to FIFRA and TSCA, and explains the scope of coverage and procedures for review of these products under both statutes. The following questions are addressed in this notice:

1. What microbial products are subject to review under FIFRA and how will they be reviewed? (Unit II)

2. What microbial products are subject to review under TSCA and how will they be reviewed? (Unit III)

3. What definitions will be used to identify the products that will be addressed by the appropriate statute? (Unit IV)

In reviewing products, the Agency is required under both FIFRA and TSCA to consider the potential benefits to society as well as any potential risks. EPA will take both risks and benefits into account in its regulatory decisions concerning these products, and will implement the two statutes in as consistent a fashion as possible within statutory constraints.

B. Background

1. *December 1984 proposal.* EPA issued for comment a "Proposed Policy Regarding Certain Microbial Products" as part of the Office of Science and Technology Policy's "Proposal for a Coordinated Framework for Regulation of Biotechnology." This proposal was published in the **Federal Register** of December 31, 1984 (49 FR 50880) and is hereafter referred to as the "December 84 notice." Briefly, in the December 84 notice EPA proposed a mechanism for review of genetically engineered and nonindigenous microbial pesticides under FIFRA. It also described how EPA proposed to address certain genetically engineered microorganisms subject to the new chemical substance premanufacture notification (PMN) provisions of section 5 of TSCA.

2. *Comments on the December 84 notice.* EPA received comments on the December 84 notice from 68 organizations and individuals. All the comments received by EPA are available for review and copying from 8 a.m. to 5 p.m. Monday through Friday, except legal holidays, in the TSCA Public Information Office, Rm. E–107, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460.

The Agency has carefully evaluated these comments. Several of the proposed policies set forth in the December 84 notice have been revised or clarified in this notice in response to these comments and as a result of the regulatory experience EPA has gained over the past year.

One of the most frequent comments addressed EPA's authority under TSCA and FIFRA. The Agency has continued to evaluate the extent and limit of its statutory authority and has concluded that TSCA and FIFRA provide sufficient authority for the Agency to meet its goals and responsibilities in regulating biotechnology products. However, some new regulations will be required and others will have to be modified in order to fully implement certain aspects of EPA's policies. These regulations and modifications are discussed in Units II and III of this notice.

Numerous commenters addressed the scope of EPA's policy and raised questions about which microbial products are subject to TSCA and FIFRA. In Units II.B, and III.B, the Agency provides detailed explanations of which microorganisms are and are not subject to FIFRA and TSCA, and from among the products that are subject, which are subject to regulatory review prior to any environmental application.

Many commenters expressed concern that the Agency was relating a microorganism's potential for risk to the process by which it was made, particularly in the definition of which microorganisms are "new" and therefore subject to PMN under TSCA. First, commenters suggested that the process by which an organism was modified was too indirect as an indicator of its newness. They pointed out that while certain processes can be used to produce new combinations of traits in microorganisms, their use does not necessarily mean that new combinations of traits have been formed. Second, the process-based approach was believed to be an insufficient indicator of risk, because genetic engineering processes do not necessarily produce organisms that present risks, nor are non-engineered organisms necessarily safe. Finally, because the process-based approach would single out certain techniques for regulation, it would result in market distortions that favored the more traditional techniques even though the newer techniques could be as safe or safer.

After reviewing the comments, the Agency considered a number of alternatives to the "process-based" approach. In choosing among these alternatives, EPA carefully considered how well the options approximated risk (there was uncertainty with all the options in this respect), whether they could be implemented and enforced through criteria that were unambiguous to all affected persons, and (in the case of organisms subject to TSCA) the TSCA mandate to review "new" substances. The alternative EPA has chosen gives particular attention, under both FIFRA and TSCA, to microorganisms that (1) are used in the environment, (2) are pathogenic or contain genetic material from pathogens, or (3) contain new combinations of traits (e.g., organisms that are genetically modified to contain genetic material from dissimilar source organisms and organisms that are nonindigenous). EPA believes these categories have sufficiently high potential for widespread exposure, adverse effects, or uncertainty concerning potential effects to deserve particular regulatory scrutiny. This approach takes a significant step towards separating products on the basis of potential risk.

The Agency also received comments on the information and data to be submitted by companies filing notifications of intent to conduct field tests with certain microbial pesticides. These requirements have been clarified and additional references have been cited in the FIFRA unit of this notice that should provide useful guidance on what information to submit. The TSCA unit contains similar guidance on the submission of information.

Finally, several commenters addressed issues pertaining to confidential business information (CBI). Some expressed concern that CBI be adequately protected from disclosure, while others stressed the need for public access to information on new biotechnology products. EPA has summarized its position with respect to CBI and public disclosure later in this overview (Unit I.G).

A background document providing more detail on the Agency's response to comments on the December 84 notice has been placed in the public record for this notice and is available in the TSCA Public Information Office (address listed in Unit VI of this notice).

C. Summary of EPA Policy

This notice focuses on oversight and review procedures for microorganisms that are subject to FIFRA or TSCA. Microorganisms intended for use as pesticides are subject to FIFRA, and many microorganisms intended for general commercial and environmental applications (e.g., metal leaching, pollutant degradation, enhanced nitrogen fixation) are subject to TSCA. This notice addresses the rationale for various requirements and provides guidelines for compliance.

Specifically, EPA's policies that apply to microbial products subject to FIFRA or TSCA jurisdiction will include the following specific requirements:

1. Microorganisms deliberately formed to contain genetic material from dissimilar source organisms (inter-generic) will be subject to review before any environmental releases, including small-scale field testing and other environmental research and development (R&D). Under the statute, those that are subject to TSCA and used in closed systems (i.e., never intentionally released to the environment) must be reported before they are manufactured for non-R&D commercial purposes. However, EPA is considering promulgating a rule to exempt certain contained uses from this requirement.

2. Microorganisms formed by genetic engineering other than inter-generic combinations will be subject to the following provisions: (a) if any source organism is a pathogen, the resulting microbial products are subject to review under FIFRA or TSCA prior to any environmental release, except if used solely for non-pesticidal agricultural uses, in which case they are subject only to U.S. Department of Agriculture (USDA) review (see the USDA notice in this **Federal Register**) (b) if source organisms are not pathogens, the resulting microbial products are subject to abbreviated review under FIFRA (if they are pesticides) before any small-scale environmental release, or will be subject to the reporting requirements of sections 8 (a) and (e) of TSCA.

3. Nonengineered microorganisms: (a) indigenous pathogens will be reviewed under FIFRA or TSCA prior to use on greater than 10 acres of land and greater than 1 acre of water, except those that are solely for non-pesticidal agricultural purposes, which will be subject only to USDA authority; (b) nonindigenous pathogens will be reviewed under FIFRA prior to any environmental release, and under TSCA prior to release at greater than 10 acres, unless they are pathogens used solely for non-pesticidal agricutural purposes in which case they will be reviewed by USDA (see USDA notice in this **Federal Register**); (c) nonindigenous microbial pesticides that are not pathogens will be subject to abbreviated review under FIFRA before any small scale environmental release; (d) indigenous microbial pesticides that are not pathogens will be reviewed under FIFRA prior to use on greater than 10 acres.

4. All other microorganisms used or intended for use as pesticides and not covered in Unit I.C. 1 through 3, regardless of source, mode of action, or method of manufacture will be reviewed under FIFRA prior to use on greater than 10 acres unless exempted by regulation.

5. Manufacturers and importers of microorganisms under TSCA, if they are not otherwise subject to review, will be required to submit general information, before environmental release, that the Agency can use to monitor environmental uses and to determine if additional requirements are necessary in the future. EPA will gather such information by means of a TSCA section 8(a) reporting rule.

6. Manufacturers and importers of all microorganisms subject to TSCA must report any information on substantial risks under TSCA section 8(e). Registrants of microbial pesticides must report any information regarding unreasonable adverse effects of the pesticide on the environment under FIFRA section 6(a)(2).

A table at the end of Unit I summarizes the policies for prior notification and review of microorganisms applied in the environment.

This policy is immediately effective for microbial pesticides under FIFRA and for "new" microorganisms subject to premanufacture notification under TSCA. Implementing other aspects of the policy for TSCA substances, however, will require rulemaking. Until final rules are effective, EPA expects manufacturers to comply with most aspects of the policy voluntarily. The one exception is that manufacturers of microorganisms, described in Unit I.C.5, that are excluded from other TSCA notification requirements are not expected to report until a final section 8(a) rule is promulgated.

This notice also describes the types of information EPA expects to receive from persons subject to these policies to permit an evaluation of possible risks. EPA will determine specific information needs on a case-by-case basis, and will frequently use non-Agency experts with specific knowledge of the relevant microorganisms and uses to assist in reviews. In addition, EPA is establishing a biotechnology Science Advisory Committee (SAC) to provide peer review of specific cases and advice on technical issues. The SAC will be composed of non-Agency scientists and members of the lay public. More information on the SAC may be found in Unit I.F.

Although many of the policies described in this notice are immediately effective, the Agency recognizes that biotechnology is a repidly developing field and that newly available information may affect the judgments underlying these policies. Accordingly, EPA recognizes that modifications of these policies may be necessary in the future, and it is willing to make such modifications as may be appropriate. Therefore, EPA encourages all interested persons to provide comments on the policies described in this notice. Comments should be submitted to the address provided at the beginning of this EPA notice. The public will have additional opportunities for comment when the Agency proposes rules for those parts of its policy that require rulemaking procedures. Thse parts are specifically indicated in Units II and III.

D. Rationale for Approach

This unit provides a discussion of EPA's rationale for giving special focus to environmental release, pathogens, and microorganisms with new characteristics (e.g., containing genetic material from dissimilar source organisms or nonindigenous organisms).

1. Environmental releases. Physical containment can be used to mitigate undesirable or unexpected characteristics of a microorganism by providing the means to control a microorganism's growth, reproduction, and exposure to other organisms. However, microorganisms meant to be released in the environment are not subject to this control mechanism. Although many microorganisms will be biologically contained, that is, they will have existing and inherent limitations on their growth and survival, some of them may reproduce and thereby increase in number in the environment beyond the amounts originally released. Some will also have independent mobility, or may be spread beyond the area in which they are used. Thus, to ensure that environmental releases of microorganisms do not pose unreasonable adverse effects, the Agency has determined that it should review and evaluate proposals for certain environmental releases before they are allowed to proceed. The microorganisms to be subject to review before any environmental release are described in the following paragraphs, and in Units II and III of this notice.

The Agency acknowledges the difficulty of defining environmental release. For now, the Agency's approach will focus on when an organism is considered to be contained rather than when it is released. Guidance is provided in Unit IV on how to determine whether a microorganism is considered to be contained. The definition of environmental release will be refined in subsequent rulemaking activities.

2. *Pathogenic microorganisms.* Given their ability to cause disease in plants,

animals, humans, and microbes, EPA generally believes pathogenic microorganisms should be reviewed before they are released in the environment.

As used in this notice, a "pathogen" is a microorganism that has the ability to cause disease in living organisms. This includes previously documented pathogens, and microorganisms deliberately formed to contain genetic material from pathogens (e.g., through genetic engineering techniques). A complete discussion of the definition of pathogenicity is included in Unit IV, as well as guidance to aid in the determination of whether a particular microorganism falls within the scope of the EPA policies that address pathogens.

Pathogens are a clearly defined category of organisms known to cause adverse effects. In addition, because of the increased uncertainty about behavioral changes that may be associated with genetically engineered pathogens, the Agency has decided to review genetically engineered pathogens prior to any environmental release (including small-scale field testing). However, the Agency will defer review of nonengineered indigenous pathogens until they are used in larger scale applications (greater than 10 acres), because ample experience indicates that nonengineered, indigenous pathogens are sufficiently well controlled by natural mechanisms in small-scale environmental applications. Further, the Agency will not review pathogens used solely for non-pesticidal agricultural purposes (except those formed through inter-generic combinations, which are "new") because these are adequately reviewed by the USDA (see the USDA notice in this **Federal Register**).

The Agency's decision to focus on pathogens does not mean that EPA has concluded that nonpathogens are necessarily safe or that all pathogens present unreasonable risks. In fact, the Agency expects to identify widely varying degrees of risk among different uses of pathogens. It should be clear that other considerations besides pathogenicity will affect the evaluation of risk, e.g., functions of the recombined genes, possibilities for genetic transfer, environmental fate, and potential competition with other organisms. When other considerations indicate that it is appropriate, the Agency will consider excluding specific categories of pathogens from review, or may provide guidance that would limit the information requirements associated with its reviews of pathogens. As explained in Unit IV, the Agency has already exempted from review as pathogens organisms that incorporate only certain genetic material from pathogens.

3. *Microorganisms with new characteristics.* A third factor that makes potential adverse effects of microorganisms less predictable is the existence of new traits or characteristics. These traits may be new to the organism, or new to the environment in which the organism is released.

a. *Microorganisms having significant potential to exhibit new traits.* Modern genetic engineering techniques permit genetic material to be intentionally combined in organisms that would not normally share that genetic material. Some of these genetically engineered microorganisms may exhibit new or altered traits affecting, for example, their survivability, host range, substrate utilization, competition with other organisms, or protein or polysaccharide production. In some cases such microorganisms may be able to evade or overcome natural controls on their growth, or controls on their ability to cause adverse effects. In many other cases, their natural hardiness will be reduced.

In addition to the possibility that certain engineered organisms may exhibit new traits, if they are released they may be transported through natural dispersal mechanisms to other areas in the environment that have not previously contained organisms having these new combinations of traits.

Because of these considerations, EPA's policies will give particular regulatory attention to organisms that have a significant probability of exhibiting a new trait or combination of traits (standards for this are explained below). This approach accomplishes two important objectives. First, it identifies a group of microorganisms whose behavior in the environment poses significant uncertainty and thus warrants regulatory review. Simultaneously, it provides a way of defining "new" microorganisms that are subject to PMN requirements under TSCA (see Unit III.C.1).

EPA's policy, specifically, focuses on microorganisms that have been deliberately altered to contain genetic material from dissimilar source organisms, because such organisms are more likely to exhibit new combinations of traits and their behavior is therefore less predictable. Given this conceptual basis, the question then becomes how dissimilar two organisms must be before combinations of genetic material between them are likely to produce "new combinations of traits."

Based on the following considerations, EPA has decided that inter-generic combinations (combinations from source organisms of different genera) but not intra-generic combinations (source organisms from the same genus) are sufficiently likely to result in new combinations of traits that they should be given special attention. First, combinations of genetic material from microorganisms from different genera are more likely to result in new traits than combinations of genes from microorganisms within the same genus. Also, while genetic exchange occurs naturally and somewhat commonly among many microorganisms, it is more likely to occur in nature within a single genus than across many different genera (Refs. 2, 12, 13). Finally, genus designations provide a practical criterion for administrative and regulatory purposes.

The Agency has decided to exclude certain combinations from special consideration as inter-generic organisms. Excluded are inter-generic combinations in which the genetic material added to the recipient microorganism consists only of well-characterized, non-coding regulatory regions. The resulting organisms do not possess new combinations of traits; rather, they exhibit quantitative changes in preexisting traits. In addition, if experience or data indicate that certain other inter-generic combinations warrant exclusion, the Agency will use the appropriate statutory or policy mechanisms under FIFRA and TSCA to waive certain requirements for reviewing them. For example, EPA is considering exempting from PMN review under TSCA those inter-generic combinations used only in physically contained systems.

Although EPA considers intra-generic combinations to be less likely to produce new combinations of traits than inter-generic combinations, the Agency realizes that science provides no absolute standard for such distinctions. Nevertheless, EPA believes the approach it has adopted is practical and facilitates the identification of those microorganisms that should be subject to special attention and also that should be considered "new" under TSCA. If experience reveals that intra-generic combinations that could cause adverse effects will be developed, the Agency will modify its policies to require review of these products.

Unit IV contains more detailed guidance for determining if a given microorganism is the result of an inter-generic combination. The determinations are based on taxonomic

designations of organisms. The Agency is aware that microbial taxonomy is a dynamic and often controversial science (Refs. 4. 18) and that new information concerning microorganisms' properties and interrelationships will alter taxonomic designations. However, the Agency believes that its procedures can be sufficiently flexible to accommodate the developments that will occur, and that there are many significant advantages to using taxonomic standards. These advantages are discussed in more detail in Unit IV.

b. *Nonindigenous microorganisms.* Another category of organisms that are likely to exhibit traits new to an environment is nonindigenous microrganisms. Application of nonindigenous microorganisms in the environment could pose a high degree of uncertainty with respect to their behavior. Experience shows that scientists cannot always accurately predict how such organisms will behave in their new environment (Ref. 15, 16). It can be difficult to predict whether a nonindigenous microorganism will be subject to the physical and biological control factors present in the environment where it is to be introduced. In a small number of cases, nonindigenous pathogens such as the chestnut blight fungus and the Dutch elm disease fungus have caused significant adverse effects. As a result, there exist today regulations that govern the intentional movement of some, but not all, nonindigenous species (e.g., the Plant Pest Act administered by USDA). EPA believes that nonindigenous microorganisms whose uses are covered by FIFRA should be subject to Agency review and evaluation before they are released in the environment, to minimize the uncertainties with respect to their behavior. However, EPA does recognize that small-scale use of certain nonindigenous microbial pesticides (i.e., pathogens) may pose greater potential risk than others, and has accordingly adopted abbreviated review procedures for small-scale use of nonpathogenic nonindigenous microbial pesticides. Unit II addresses these issues, and Unit IV provides guidance on determining whether a microorganism is nonindigenous.

E. Explanation of Jurisdiction—EPA and USDA

Both EPA and USDA seek to assure the safety of microbial products and yet minimize impediments to intellectual and economic advances in biotechnology. Because some of the statutes the agencies administer entail overlapping responsibilities, the two agencies are eliminating duplicative requirements wherever possible and coordinating their reviews.

Where allowed by statute, EPA and USDA have sought to eliminate overlapping reviews altogether. This notice reflects many instances where this has been done. Where overlaps could not be avoided, the agencies have established mechanisms for coordinating their reviews. EPA and USDA will identify principal liaisons who will have the responsibility to share information, coordinate data requests, and keep one another informed of communications with submitters. Also, the agencies will form a coordinating committee to meet periodically and work out general coordination problems that may transcend specific reviews. Finally, the National Biological Impact Assessment Program that has been established within USDA will provide a common resource of scientists available to both agencies to review procedures, protocols, and projects on an advisory basis.

Submitters are encouraged to contact either agency if they have jurisdictional questions, but general guidelines are described below.

First, inter-generic microorganisms containing genetic material from a pathogenic source organism must be reported to both agencies (definitions of "inter-generic" and "pathogen" may be found in Unit IV). In this case, statutory constraints make it necessary for both EPA and USDA to review the products because the microbes are potential "pests" subject to the Plant Pest Act, and they are "new" and therefore subject to TSCA premanufacture notification (or they are pesticides and subject to FIFRA notification). However, the agency reviews have somewhat different purposes, in that the EPA review is for a general use of an organism under TSCA or for use as a pesticide under FIFRA, while the USDA review is for a specific permit application. The agencies will coordinate these reviews as explained earlier.

Second, persons developing inter-generic organisms that contain no genetic material from a pathogen and that do not meet the USDA definition of a "plant pest" will be expected to report only to EPA; they will not report to USDA at all. EPA will inform USDA and the submitter if any data suggest that the organism has pest qualities which may require a permit from USDA. This avoids unnecessary duplication of effort and is consistent with the non-discretionary responsibility under TSCA to review new organisms and under FIFRA to review pesticides.

Third, in the case of intra-generic engineered organisms that contain genetic material from a pathogen, the use of the organism will determine which agency reviews it. When used solely for non-pesticidal agricultural purposes, such organisms must be reported only to USDA under the Plant Pest Act. When used for non-agricultural purposes, such organisms should be reported to EPA, either voluntarily under the TSCA section 5(a)(2) rule EPA will be developing or, if the organism is a pesticide, under FIFRA. In both cases, the microorganisms should also be reported to USDA as potential plant or animal pathogens. When such dual reporting is necessary, the agencies will assist the submitter by coordinating through the mechanisms described above.

In the case of intra-generic microbes containing no genetic material from pathogens and nonengineered microorganisms, EPA will gather general information under section 8(a) of TSCA and conduct abbreviated reviews under FIFRA (see Units II and III of the EPA notice). Both agencies agree that members of this category of microbes, in general, present the lowest risk and therefore do not need a high level of scrutiny before any release into the environment. However, the FIFRA abbreviated reviews and the TSCA section 8(a) reporting will ensure that both agencies are aware of environmental releases of these organisms and can take appropriate action when necessary.

F. EPA Biotechnology Science Advisory Committee

EPA is establishing a Science Advisory Committee for biotechnology. The formation of this committee is consistent with intentions stated in two **Federal Register** notices issued by the Office of Science and Technology Policy (49 FR 50904, December 31, 1984 and 50 FR 47174, November 14, 1985). The committee's primary functions will be to provide peer review of specific product submissions under TSCA, FIFRA, and other EPA statutes and scientific oversight of the Agency's biotechnology programs.

The committee will consist of independent scientists and members of the lay public. It will be of sufficient size and diversity to provide the range of expertise required to assess the scientific and technical issues pertinent to its responsibilities. The committee will be supplemented by consultants when they are needed to extend the range of expertise of the standing committee, and will be authorized to

form subcommittees or panels for any purpose consistent with its charter.

Scientific members of the committee will be selected on the basis of their professional qualifications to examine the questions of hazard, exposure, and risk to humans, other non-target organisms, and ecosystems. Some committee members will serve as liaisons (holding joint membership) with the FIFRA Scientific Advisory Panel (SAP) and with the EPA Science Advisory Board (SAB). The SAC will also include nonvoting representatives from other Federal agencies that are involved in regulating products of biotechnology.

The Agency intends for meetings of the SAC to be open to the public. Meetings may be closed by the Chairperson when necessary, such as during discussion of issues subject to statutory confidentiality requirements, but EPA will encourage open public discussion of issues to the greatest extent possible (see unit I.G).

G. Confidential Business Information

Both FIFRA and TSCA generally prohibit the Agency from releasing certain confidential business information (CBI). These prohibitions apply to information on products of biotechnology, and the Agency will meet its obligations to protect information claimed confidential by applicants and other data submitters. However, the Agency also recognizes that there is strong public interest in many aspects of biotechnology, particularly in the possibility of adverse effects resulting from the environmental release of genetically engineered organisms. Accordingly, it is the Agency's policy to carry out as much of its review as possible in the open, in order to provide an opportunity for public participation and to increase public confidence in the review process. The Agency is encouraged by the extent to which industry and other submitters have been willing to authorize the release of relevant information to date and urges future data submitters to limit confidentiality claims as much as possible in order to foster an open review process.

H. International Aspects

EPA is committed to the policy described in the section entitled "International Aspects" in the Office of Science and Technology Policy Preamble, published in this **Federal Register.**

SUMMARY TABLE.—PRIOR NOTIFICATION AND REVIEW OF MICROORGANISMS APPLIED IN THE ENVIRONMENT

[Coverage by notification and review policy [1]]

Type of microbial product	FIFBRA		TSCA	
	< 10 acres	>10 acres	< 10 acres	> 10 acres
1. Genetically engineered microorganisms				
a. Formed by deliberate combinations of genetic material from dissimilar source organisms (inter-generic combinations).	X	X	X	X
b. Formed by genetic engineering other than inter-generic combinations				
i. pathogenic source organisms [2]	X	X	X	X
ii. nonpathogenic source organisms	O	X	O	O
2. Nonengineered microorganisms				
a. Nonindigenous pathogens [2]	X	X	O	X
b. Nonindigenous nonpathogens	O	X	O	O
c. Indigenous pathogens [2]		X	O	X
d. Indigenous nonpathogens		X	O	O

[1] "X" designates that the microorganism will be subject to EPA review prior to small-scale (10 acres or less) or large scale (greater than 10 acres) environmental applications, as indicated. Under TSCA, submitters would only notify the Agency once (at the first appropriate time), unless during the original review EPA specifies that further reporting is required.
"O" designates that the microorganism will be subject to abbreviated review prior to small-scale (10 acres or less) or large scale (greater than 10 acres) environmental applications, as indicated. Under FIFRA, this provision is effective immediately. Under TSCA, the abbreviated notification will be implemented through rulemaking.
[2] Pathogens in this category used solely for non-pesticidal agricultural purposes will not be subject to EPA notification requirements. They will be subject only to USDA review. See Unit IV for a definition of "agricultural uses" and "pathogens."

II. Applicability of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to Microbial Products

A. Background

Biological agents, including microorganisms, may be used as pesticides, and as such they are subject to regulation under FIFRA unless specifically exempted by regulation. FIFRA establishes EPA's authority over the distribution, sale, and use of pesticide products. Before EPA can register a pesticide, it must have sufficient data to determine that the product, when used in accordance with widespread and commonly recognized practice, will not cause (or significantly increase the risk of) unreasonable adverse effects to humans or the environment. In recent years, the Agency has put in place policies, procedures, and regulations to address the human health and environmental concerns raised by the application of biological pesticides (including genetically engineered and nonindigenous microbial products) in the environment. This unit outlines EPA's regulatory mechanism for these products and updates its policy on small-scale field testing of microbial pesticides.

Regulations promulgated under FIFRA and appearing at 40 CFR 162.5(c)(4) specify that microorganisms, when used as pesticides, are regulated under FIFRA. The specific kinds of data and information that are required to support the registration of each microbial pesticide under FIFRA are detailed in 40 CFR 158.65, 158.170, and 162.163. The Agency has also published guidance for developing these data in the Pesticide Assessment Guidelines: Subdivision M—Biorational Pesticides (Ref. 20).

The Agency must conduct a complete evaluation and review of the data submitted to support any pesticide registration before determining whether the pesticide should be registered. This evaluation is conducted with respect to the general criteria set forth in 40 CFR 162.7(d) and (e) and 162.167. Prior to registration, producers may test their pesticide products under an experimental use permit (EUP), issued pursuant to section 5 of FIFRA and 40 CFR Part 172. The data and information needed to support the issuance of an EUP for microbial pesticides are specified at 40 CFR 158.170.

The regulations governing EUPs include a generally applicable presumption that EUPs will not be required for certain small-scale experimental uses of new pesticides (or new uses of previously registered pesticides). Recently, however, the Agency issued a statement of interim policy on small-scale field testing of nonindigenous and genetically altered microbial pesticides, published in the **Federal Register** of October 17, 1984 (49 FR 40659); see also 49 FR 50882, December 31, 1984. Briefly, the policy statement announced that the small-scale field test provision of 40 CFR 172.3 would not automatically apply to, and that the Agency should be notified before the initiation of, any field testing of genetically altered or nonindigenous microbial pesticides to determine if EUPs are required. This policy is being revised by this notice and is discussed in detail in Unit II.D.

B. Scope of FIFRA

1. *Pesticides addressed by this notice.* All pesticides whose active ingredient(s) consist of microorganism(s) (i.e., all microbial pesticides) are addressed by

this notice. Microbial pesticides may include bacteria and blue-green algae, fungi, viruses, and protozoa used as pest control agents.

2. *Pesticides not addressed by this notice.* The Agency has determined that certain nonmicrobial organisms which fall within the definition of biological control agents are already addressed by other agencies, specifically USDA and the Department of the Interior. Examples of these biological control agents are vertebrates, insect predators, nematodes, and macroscopic parasites. Therefore, pursuant to section 25(b) of FIFRA and 40 CFR 162.5(c)(4), these nonmicrobial biological control agents have been exempted from regulation under FIFRA. However, if EPA, in cooperation with other agencies, determines that certain biological control agents exempted by § 162.5(c)(4) are not being adequately regulated, these organisms will be referred to the attention of the appropriate agency or added to the exceptions in § 162.5(c)(4) by amendment. In the latter case, those organisms would no longer be considered exempt from the provisions of FIFRA.

This unit of the notice does not address any chemical pesticide product or byproduct produced by microorganisms. Such chemicals are covered under current pesticide regulations, registration procedures, data requirements, and testing guidelines (see 40 CFR Parts 158 through 180; and Subdivisions D through O of the Pesticide Assessment Guidelines).

3. *Information-gathering policy.* In order to expand its level of knowledge and expertise, monitor the industry, and determine whether its current policy needs modification, the Agency needs as complete a data base as possible. Accordingly, those developing microbial products intended for use as pesticides that are not otherwise subject of FIFRA review are encouraged to keep the Agency apprised of their activities. In addition, registrants of microbial pesticides are reminded that, pursuant to FIFRA section 6(a)(2), they must report any information regarding unreasonable adverse effects of the pesticide on the environment.

C. Microbial Pesticides—History and Long-Term Regulatory Strategy

1. *History.* Microbial pesticides have been in use for many years. In 1948, the Federal Government registered the first such product, *Bacillus popilliae*, to control Japanese beetle larvae in turf. However, it was not until the late 1960s and early 1970s that interest in microbial pesticides began to increase. At that time, EPA began to develop policies and procedures to specifically address microbial pesticide products. In 1983, EPA's Office of Pesticide Programs issued testing guidelines for microbial pesticides (Ref. 20). A year later, EPA issued a final regulation (40 CFR Part 158) specifying the data requirements for pesticide registration (including genetically engineered microbial pesticides). As of 1985, there were 14 microbial pesticides used in several hundred separate products registered for use in agriculture, forestry, mosquito control, and homes.

As indicated in Unit II.A above, EPA issued an interim policy on small-scale field testing of genetically altered and nonindigenous microbial pesticides in October 1984 (49 FR 40659). To date, under this policy, EPA has received and reviewed five notifications for genetically engineered microbial pesticides and two notifications for nonindigenous microbial pesticides. Three EUP applications, required in part to address unresolved issues identified in the review of these notifications, have since been received. These applications were for genetically engineered microbial pesticides.

2. *Long-term regulatory strategy.* Although EPA has an established regulatory mechanism for microbial pesticides, the Agency envisions some further modifications in the future to specify certain policies in more detail, keep the assessment process current with existing scientific knowledge, and ensure an efficient review mechanism. Some of these anticipated modifications are discussed here.

As noted in Unit I, EPA intends to revise the EUP regulations (40 CFR Part 172) to incorporate the concepts embodied in the interim policy on small-scale field testing. Specifically, Part 172 will be revised to specify more clearly which applicants must notify EPA before conducting small-scale field tests with microbial pesticides and the content of notification.

As noted in the overview to this EPA notice (Unit I.F), EPA is forming a Science Advisory Committee. The Scientific Advisory Panel, an advisory group mandated by FIFRA, will continue to serve in its advisory capacity on specific submissions under FIFRA, until the SAC is formed.

FIFRA requires EPA to review and periodically update its guidelines, and OPP has begun this process for the Subdivision M Pesticide Assessment Guidelines. The Guidelines are currently being revised to reflect current testing methodology and advances in risk assessment capabilities resulting from OPP's recent experience in evaluating genetically engineered microbial pesticides. In addition, as the Agency gains risk assessment experience and assembles a larger body of risk assessment data, it may be appropriate to amend the Part 158 data requirements regulation to add to or modify the data requirements that apply to genetically engineered and nonindigenous microbial pesticides.

D. Regulatory Review of Microbial Pesticides

This unit describes EPA's data requirements and review procedures for microbial pesticides. In particular, Unit II.D.1 describes the requirements and review plan for those microbial pesticides subject to review under FIFRA before they may be used in any application in the environment (i.e., small-scale field testing). Unit II.D.2 outlines the regulatory review for those microbial pesticides subject to the FIFRA requirements for an experimental use permit or registration. In most instances, microbial pesticides subject to the provisions in Unit II.D.1 will also be subject to the provisions in Unit II.D.2 when they are to be used for larger scale or commercial purposes in the environment.

1. *Small-scale field testing.* Prior to obtaining a registration for a pesticide product, applicants generally need to conduct field studies in order to gather product performance, use, and other types of data necessary to support the registration of their product. The regulations governing field studies (40 CFR Part 172) include a generally applicable presumption that EUPs will not be required for certain small-scale uses of new pesticides (or new uses of previously registered pesticides). The Agency issued a statement of interim policy addressing small-scale field testing of microbial pesticides in 1984. The interim policy announced that the Agency should be notified before initiation of any field testing of genetically altered or nonindigenous microbial pesticides. The purpose of this policy is to provide a mechanism for the Agency to evaluate these proposed small-scale field tests for possible risk to human health or the environment and determine whether EUPs are required before the tests can be initiated.

Small-scale field studies are (1) terrestrial field studies that involve 10 acres or less of land; and (2) aquatic field studies that involve 1 surface acre or less of water.

To minimize the regulatory burden on producers of genetically engineered and nonindigenous microbial pesticides, and more closely correlate the level of Agency review with potential risk of the

microorganism, the Agency has adopted a two-level review system based on its evaluation of the potential risks posed by various types of microorganisms. The two-level system will allow the Agency to receive some basic information on small-scale testing of genetically engineered and nonindigenous microorganisms that are less likely to pose significant risks to humans or the environment (Level I reporting), while reserving full notification and review procedures for microorganisms about which there is more concern (Level II notification). The review system is designed so that producers of microbial pesticides may proceed with their small-scale field tests without Agency approval, unless they are notified within a specified time that additional information or an EUP is required. In the case of level I reporting, producers need only provide a limited amount of information, and are assured of an expedited response from the Agency if it is determined that additional information is required.

The two-level system is based on the analysis set forth at Unit I.D, in which the Agency has defined groups of microorganisms that raise more concerns about their likelihood to pose risks to humans or the environment, when released into the environment, than other microorganisms. Specifically, these include microbial pesticides formed by deliberately combining genetic material from organisms of different genera and genetically engineered or nonindigenous microbial pesticides derived from pathogenic source organisms. However, other genetically engineered and nonindigenous microbial pesticides are less likely to pose significant risks to humans or the environment when applied in small-scale field test. Accordingly, the Agency has determined that this second category of microbial pesticides will be subjected to a reporting requirement and will be reviewed as described in Unit II.D.1 a through c below. The Agency will have up to 30 days to review the reported information. The kind of information needed to fulfill the reporting requirement is typically already available to an applicant as an essential part of product research and development, and is not generally expected to require generation of new data.

All microbial pesticides formed by deliberately combining genetic material from organisms of different genera, and all genetically engineered or nonindigenous microbial pesticides derived from pathogenic source organisms will be subject to the full notification requirements (Level II) as described in Unit II.D.1.e below. The Agency has determined that these organisms should continue to be subjected to the full notification and review procedures set out in the original interim policy published on October 17, 1984. The Agency will have up to 90 days to review a Level II notification.

The scope and requirements for Level I reporting and Level II notification are detailed below. The interim policy as revised by this notice does not apply to studies conducted under enclosed, contained conditions, as defined in Unit IV.

a. *Level I reporting.* Level I reporting for small-scale field testing applies to all genetically engineered or nonindigenous microbial pesticides not otherwise covered by Level II notification as detailed in II.D.1.d below. Small-scale field tests of additional groups of genetically engineered and nonindigenous microbial pesticides now covered by Level II notification may also be determined to warrant only abbreviated review in the future. The Agency will make these determinations on a case-by-case basis.

b. *Level I information.* Each report should include the following information, or, where specific information is not submitted, documentation of why it is not practicable or necessary to provide the information.

(1) Identity of the microorganism, including characteristics, and means and limits of detection.

(2) Description of the natural habitat of the microorganism or its parental strains, including information on natural predators, parasites, and competitors.

(3) Information on the host range of the parental strain(s) or nonindigenous microorganism.

(4) Information on the relative environmental competitiveness of the microorganism, if available.

(5) If the microorganism is genetically engineered, information should be provided on the methods used to genetically engineer the microorganism(s); the identity and location of the rearranged or inserted/deleted gene segment(s) in question; a description of the new trait(s) or characteristic(s) that are expressed; information on potential for genetic transfer and exchange with other organisms, and on genetic stability of any inserted sequence.

(6) A description of the proposed testing program, including site location, crop to be treated, target pest, amount of test material to be applied, and method of application.

c. *Level I reporting process.* EPA will have up to 30 days to review the above information to make a preliminary determination of the need for an EUP. If the Agency does not notify the applicant of the need for an EUP within the 30 days, the applicant may proceed with the proposed field test. If, on preliminary assessment, the test raises sufficient concerns such that the Agency determines that additional information or monitoring is warranted, then an EUP will be required (e.g., microorganisms for which there is limited scientific information or regulatory experience, or that raise significant questions concerning genetic stability, competitiveness, or mode of action, or that warrant specific environmental monitoring during the test). In this case, the applicant has two options. First, the applicant may apply for a permit, providing the necessary data and information required to support the application. Alternatively, the applicant may provide all additional data and information required under Level II notification as outlined in Unit II.D.1.e below. If the latter option is chosen, the Agency will have an additional 60 days to review the full notification package and make a final determination as to whether an EUP is required.

d. *Level II notification.* Level II notification for small-scale field testing applies to microbial pesticides: Microbial pesticides formed by deliberately combining genetic material from organisms of different genera, genetically engineered microbial pesticides derived from source organisms that are pathogens (as defined in Unit IV), and nonindigenous pathogenic microbial pesticides (as defined in Unit IV).

e. *Level II requirements.* Notification should include adequate information to allow the Agency to evaluate the small-scale field testing program. Each notification should include the following information, or, where specific information is not submitted, documentation of why it is not practicable or necessary to provide the information.

(1) Background information on the microorganism.

(a) Identity of the microorganism, including tables of characteristics, and means and limit of detection using the most sensitive and specific methods available.

(b) Description of the natural habitat of the microorganism or its parental strains, including information on natural predators, parasites, and competitors.

(c) Information on host range, especially infectivity and pathogenicity to nontarget organisms.

(d) Information on survival and ability of the microorganism to increase in numbers (biomass) in the environment (e.g., laboratory or containment facility test data).

(e) If the microorganism is genetically altered, the following information should be provided in addition to the information listed in (a) through (d) above:

i. Information on the methods used to genetically alter the microorganism.

ii. The identity and location of the rearranged or inserted/deleted gene segment(s) in question (host source, nature, base sequence data, or restriction enzyme map of the gene(s)).

iii. Information on the control region of the gene(s), and a description of the new trait(s) or characteristic(s) that are expressed.

iv. Information on potential for genetic transfer and exchange with other organisms, and on genetic stability of any inserted sequence.

v. Information on relative environmental competitiveness compared to the parental strains.

(2) Description of proposed field test.

(a) The purpose or objectives of the proposed testing.

(b) A detailed description of the proposed testing program, including test parameters.

(c) A designation of the pest organism(s) involved (common and scientific names).

(d) A statement of composition for the formulation to be tested, giving the name and percentage by weight of each ingredient, active and inert, production methods, contamination with extraneous microorganisms, potency and amount of any toxins present, and where applicable the number of viable microorganisms per unit weight or volume of the product (or other appropriate system for designating the quantity of active ingredient).

(e) The amount of pesticide product proposed for use and the method of application.

(f) The State(s) in which the proposed program will be conducted, and specific identification of the exact location of the test site(s) (including proximity to residences and human activities, surface water, etc.).

(g) The crops, fauna, flora, geographical description of sites, modes, dosage rates, frequency, and situation of application on or in which the pesticide is to be used.

(h) A comparison of the natural habitat of the microorganism with the proposed test site.

(i) The number of acres, number of structural sites, or number of animals/plants, by State, to be treated or included in the area of experimental use, and the procedures to be used to protect the test area from intrusion by unauthorized individuals.

(j) The proposed dates or period(s) during which the testing program is to be conducted, and the manner in which supervision of the program will be accomplished.

(k) A description of procedures for monitoring the microorganism within and adjacent to the test site during the field test.

(l) The method of disposal or sanitation of plants, animals, soils, etc., that were exposed during or after the field test.

(m) Means of evaluating potential adverse effects and methods of controlling the microorganism if detected beyond the test area.

In addition, the following references should be consulted for further guidance on the kinds of data and information that may be relevant to the evaluation of genetically engineered microorganisms: "Proposed Points to Consider for Environmental Testing of Microorganisms" developed by the National Institutes of Health Recombinant DNA Advisory Committee Working Group on Release into the Environment (Ref. 11); "Subdivision M: Biorational Pesticides" (Ref. 20); a report by the Cornell Ecosystems Research Center titled "Potential Impacts of Environmental Release of Biotechnology Products: Assessment, Regulation, and Research Needs" (Ref. 9); a National Science Foundation Report titled "The Suitability for Environmental Applications of Biotechnology" (Ref. 3); and EPA "Points to Consider in the Microorganisms" (available from TSCA Assistance Office at the address given at the beginning of this notice).

f. *Level II review process.* Once the supporting data have been submitted, EPA has up to 90 days to review each notification of intent to conduct small-scale field testing and to determine whether an EUP is required. The Agency encourages prospective applicants to meet with EPA prior to submission of their notification to discuss their field test and determine what specific data would be necessary to evalaute the product.

EPA's review process will include some or all of the elements described in the following paragraphs. As the Agency builds a baseline of risk assessment data and gains more experience in evaluating these products, certain steps may no longer be necessary. In addition, an abbreviated review process may be appropriate in some situations (e.g., review of a proposal that is similar to an already reviewed case). Such a determination will be made on a case-by-case basis.

Once a notification is received, OPP reviews each proposal and assesses potential risks associated with the proposed experiment. OPP develops a written scientific position for each proposal which identifies potential problems or significant unanswered questions and sets forth a statement of the overall likelihood of significant risk from the proposed field testing. As the review process proceeds, it may be necessary for OPP to request supplemental information.

OPP obtains comments on its assessment from a workgroup within EPA and from other Federal agencies as appropriate (e.g., USDA, National Institutes of Health, Food and Drug Administration, and National Science Foundation). Their comments are incorporated into the scientific position, as appropriate.

OPP contacts the appropriate State pesticides regulatory authorities to ensure that they are aware of the proposal and to discuss EPA's assessment. These contacts ensure that the actions of EPA and the State agencies are as consistent as possible. OPP also notifies the Animal and Plant Health Inspection Service (APHIS) of the USDA so that they can determine whether any aspect of the proposed experiment falls within APHIS jurisdiction and, if so, to avoid duplicative or conflicting assessments.

Thus far, reviews of small-scale field testing proposals for genetically engineered microbial pesticides have emphasized some questions that have not been as significant in the assessments of naturally occurring microbial pesticides. For example, OPP has identified potential risks associated with the transfer of inserted genetic material to other organisms, the competitiveness of the engineered organism compared with the parental organisms in the environment, and the ability of the engineered organism to become established in a new ecological niche and thereby pose a potential adverse environmental impact.

OPP has addressed these and similar questions on a case-by-case basis in its risk assessments. In some cases, applicants have addressed questions by redesigning the proposed application or test microorganism to minimize the potential risk. In other instances, EPA has established data requirements and test methods as a baseline, and has designed specific laboratory test(s) (or

tiered series of tests) to establish whether the effect of concern is likely to materialize under field conditions.

If the notification raises complex or controversial scientific questions, OPP provides the notification package and its scientific evaluation to a group of independent scientists constituted as a subpanel of FIFRA's Scientific Advisory Panel. Separate subpanels may be formed to review each proposal since each microorganism and its proposed use may differ and raise questions that require the analysis of individuals with different expertise. The purpose of the SAP subpanel is to obtain an independent peer review of the OPP scientific position, to address specific scientific questions raised by OPP, and to identify any additional points, questions, or problems. As noted previously in Unit I.F, the Agency is forming a Science Advisory Committee which will assume these responsibilities in the future.

At the conclusion of the review, the Agency then decides whether an EUP is required. The decision document sets forth OPP's conclusions with respect to potential risks associated with the proposal, identifies any remaining questions or additional data that may be needed to complete the risk assessment, and, if an EUP is required, may recommend restrictions, limitations, or modifications of the proposal to address areas of concern. If an EUP is not required, the applicant may proceed with the proposed field test. If an EUP is required, the applicant must apply for a permit, providing the necessary data and information required to support the application. The Agency may decide to require an EUP to ensure that the experiment is conducted within certain defined limitations, the necessary data are developed to assess the proposal, or certain kinds of data are developed during the test and reported to the Agency.

2. *EUPs, large-scale testing, and registration.* Before a pesticide may be marketed as a commercial product, it must first be registered as provided for in section 3 of FIFRA. Large-scale field testing of a microbial pesticide is often necessary to evaluate a potential product and obtain data needed to support registration of the product. This testing, like small-scale field testing under an EUP, is subject to section 5 of FIFRA which authorizes EPA to approve applications for EUPs for limited use of an unregistered product or use of a registered product for an unregistered use. Data requirements for registration are specified in 40 CFR 158.170 and a subset of these requirements applies to large-scale field testing proposals to be performed under EUPs. The regulatory review process consists of the same basic elements in both situations and is described in this unit.

a. *Scope.* All microbial pesticides to be used in large-scale field tests are subject to review under FIFRA EUP regulations. The conditions under which an EUP is required are specified at 40 CFR Part 172, which also provides guidance on how to determine whether an EUP must be obtained. Likewise, all microbial pesticides are subject to the FIFRA registration requirements.

b. *General requirements for microbial pesticides.* The existing pesticide data requirements and regulations governing large-scale field testing (40 CFR Parts 158 and 172) and registration (40 CFR Parts 158 and 162) are applicable to all microbial pesticides, both naturally occurring and otherwise.

The agency believes that these requirements are adequate for the assessment of indigenous microbial pesticides, and provide a basis for evaluating genetically engineered and nonindigenous microbial pesticides as well. However, the Agency believes that additional data and information, determined on a case-by-case basis, may be necessary to evaluate some properties of genetically engineered and nonindigenous microbial pesticides. Part 158 explicitly provides the necessary flexibility to require additional data (§ 158.65) as well as the flexibility to waive data requirements that are not applicable (§ 158.45).

c. *Additional requirements for genetically engineered and nonindigenous microbial pesticides.* Any additional data requirements will be determined on a case-by-case basis depending on the particular microorganism, its parent microorganisms, its native habitat, the pesticide use pattern, and the manner and extent to which the microorganism may have been engineered. These additional requirements could include:

(1) Description of the natural habitat of the microorganism or its parental strains, including information on natural predators, parasites, and competitors.

(2) Information on relative ability to survive and increase in number or biomass as compared to the parental strains.

(3) Selected environmental fate tests from 40 CFR 158.170.

(4) Additional toxicology tests from 40 CFR 158.170.

(5) If the microorganism is genetically altered, then information on the genetic modification techniques used, the identity of inserted gene segment(s) (base sequence data or restriction enzyme map of the gene), the control region of the gene(s), a description of the new traits or characteristics that are intended to be expressed, and tests to evaluate genetic stability and exchange, may be required as specified previously at Unit II.D.1.b above.

d. *Review process for genetically engineered and nonindigenous microbial pesticides.* EUP applications will be reviewed in compliance with the EUP regulations under 40 CFR Part 172. The registration, reregistration, and classification procedures of 40 CFR Part 162 will be followed for registration applications. The review process will contain the same major elements as those outlined previously for small-scale field testing notifications (see Unit II.D.1.c). Briefly, this process involves scientific review and risk assessment by EPA scientists and, if appropriate, review and comment from other Federal agencies and independent expert consultants.

Once the supporting data have been submitted, EPA has up to 120 days to review an EUP application and determine whether to grant a permit. Past experience indicates that the registration process for a new microbial pesticide may vary from 9 months to several years depending upon the particular product, its use pattern, and the completeness of the registration package submitted to EPA.

Both the EUP and registration process may provide an opportunity for public comment. For example, § 172.11 of the EUP regulations specifies that if an application may be of regional or national significance the Agency will announce receipt of the application in the **Federal Register.** The announcement is accompanied by a description of the experimental program and public comments are solicited. Similarly, § 162.6 of the registration regulations specifies that if a registration application relates to a new active ingredient or a new use, notice of receipt of that application shall be published in the **Federal Register** with a request for public comment. Information on the submission is made available for public inspection.

EPA has several regulatory options for responding to either an EUP or registration application. For example, after completing its review, the Agency may determine that the field test or registration poses no unreasonable risks to humans or the environment and may grant the application. Alternatively, EPA may conclude that some additional information or data are needed to assess the potential risks adequately. In this

case, the application would be asked to provide the necessary data before EPA would decide whether to grant the application. In other cases, the Agency may impose additional limitations or restrictions on the field test or registration to address a potential risk. Finally, EPA will deny those applications where it has determined that it has all the necessary data to complete a risk assessment and that the field test or registration would pose an unreasonable risk to humans or the environment, even if additional limits or restrictions are imposed.

III. Applicability of the Toxic Substances Control Act (TSCA) to Microbial Products

A. Overview of This Unit

As discussed in the December 84 notice (49 FR 50886), EPA will review certain microorganisms and uses of microorganisms under TSCA. Microorganisms and their DNA molecules are "chemical substances" under section 3 of TSCA, and thus are subject to all the provisions of TSCA, except to the extent they are manufactured, processed, or distributed in commerce for use as pesticides, foods, food additives, drugs, cosmetics, and medical devices. For purposes of analysis and convenience of administering TSCA, EPA has chosen to focus on the microorganism as the "chemical substance."

This unit explains the statutory requirements of TSCA as they apply to microorganisms. It begins by describing which microorganisms are within the scope of TSCA and which are not. Following that are units describing five categories of microorganisms or uses of microorganisms that are or will be subject to reporting requirements under TSCA.

B. Scope of TSCA

Many organisms are not subject to TSCA requirements because of statutory exemptions; others will be exempt from certain TSCA requirements as a matter of regulatory policy. In general, the use of a microorganism determines whether it is subject to TSCA or to other laws.

Many of the comments received by OTS indicated misunderstandings of TSCA's scope. Therefore, those organisms which are and are not subject to TSCA are described in this Unit.

1. *Organisms not subject to TSCA*—a. *Microbes used as foods, food additives, drugs, cosmetics, medical devices, and pesticides.* Microorganisms are sometimes used directly as foods, food additives, drugs (including both human and animal vaccines), cosmetics, medical devices, and pesticides. When microorganisms are used for these purposes, they are explicitly excluded from TSCA and from the policies described in the TSCA portions of this notice (TSCA section 3(2)(B), 15 U.S.C. 2602(2)(B)).

Microorganisms that are used as foods, food additives, drugs, cosmetics, medical devices, and pesticides are regulated by the Food and Drug Administration (FDA), USDA, or the EPA Office of Pesticide Programs. Applicable requirements for pesticides are described in Unit II of this notice. Requirements for foods, food additives, drugs, cosmetics, and medical devices are described in the FDA and USDA notices in this **Federal Register.**

b. *Microbes used to produce foods, food additives, drugs, cosmetics, and medical devices.* In addition to being used themselves for food, drug, and other purposes, microorganisms are often used to produce chemicals that are in turn used for such purposes. For reasons explained in the December 84 notice, microorganisms will not be reviewed under TSCA when used to produce foods, food additives, drugs (including vaccines), cosmetics, or medical devices. Further information on these uses may be found in the FDA and USDA notices in this **Federal Register.**

Microorganisms used in the production of chemical end products other than foods, food additives, drugs (including vaccines), cosmetics, and medical devices are subject to TSCA. They are described in Unit III.B.3 below.

2. *Plants and animals not subject to these policies.* Plants and animals are not subject to the TSCA policies in this notice, either as whole organisms or as *in vitro* cultures for the reasons set forth in the December 84 Notice. (Definitions of plants and animals for regulatory purposes are provided in Unit IV of this EPA notice.) There are two exceptions to this general rule. First, if plant or animal gene segments are intentionally incorporated into microorganisms, the microorganisms that contain those plant or animal genes may be subject to TSCA, depending on how they are used (see Units III.B. 1 and 3). Second, a chemical extracted from a plant or animal may be subject to TSCA, again depending on how it is used. The USDA and FDA notices in this **Federal Register** contain information about regulations that apply to plants and animals.

3. *Organisms subject to TSCA—microorganisms used for purposes not excluded by law.* With the exceptions described above, all microorganisms produced for environmental, industrial, or consumer uses are potentially regulable under TSCA. It is not possible to list all the applications that could be subject to TSCA because many are yet to be developed. Some of the microorganisms that are expected in the near future and that would be subject to TSCA include microorganisms used in conversion of biomass for energy, pollutant degradation, enhanced oil recovery, metal extraction and concentration, and certain non-food and non-pesticidal agricultural applications, such as nitrogen fixation.

Microorganisms used in the production of a chemical end product will be subject to TSCA if the end product is any chemical substance used for a purpose other than as a food, food additive, drug, cosmetic, or medical device. For example, microorganisms are subject to TSCA if they are used in the production of pesticides, fuels, solvents, dyes, cleansing agents, etc. TSCA jurisdiction over such microorganisms, which may be used entirely in closed manufacturing systems, is consistent with TSCA coverage of conventional chemicals. For example, chemical intermediates—even those used in closed systems—fall under TSCA authority and are subject to PMN requirements if new (40 CFR Part 720). Similarly, as described in Unit III.C.1 of this notice, "new" microorganisms used in chemical production are subject to PMN requirements.

4. *Chemicals produced by microorganisms—Status under TSCA.* Although the purpose of this notice is to provide information on the applicability of TSCA to microorganisms, some readers may wish to obtain information on requirements that apply to chemicals produced by microorganisms. For example, various proteins and polysaccharide gums are produced by microorganisms and may be subject to TSCA, depending on how they are used (see Unit III.B.1). These chemicals produced by microorganisms are subject to the same requirements and procedures as chemicals produced by other means. Any special concerns pertaining to the microbial production method, such as the possibility of contaminants, will be considered during the review of the microorganisms used in producing the chemicals. This approach is explained in the December 84 notice at page 50890.

C. Specific Requirements Under TSCA

The fact that a microorganism is potentially subject to TSCA does not necessarily mean that it will be regulated under TSCA. The rest of this unit explains the specific provisions that apply or will apply to various types of

microorganisms falling within TSCA's jurisdiction.

In overview, microorganisms are (or will be) subject to TSCA requirements in the following manner:

As of the date of this notice, microorganisms that are subject to TSCA and contain genetic material from dissimilar source organisms (i.e., organisms from different genera) are subject to PMN requirements.

Microorganisms other than inter-generic combinations that are subject to TSCA and are pathogenic or contain genetic material from pathogens, will in the future, if released into the environment, be subject to "significant new use" reporting requirements under TSCA section 5(a)(2). One exception is that agricultural uses of such microorganisms will be reviewed by USDA rather than EPA. EPA expects voluntary notification to begin immediately for uses that will be subject to significant new use reporting requirements.

The research and development exemption from PMN and significant new use notification requirements will be amended so that it no longer applies to microorganisms released to the environment. EPA expects voluntary notification of such uses to begin immediately.

EPA will issue a rule requiring manufacturers and importers to submit general information on environmental uses of microorganisms that are subject to TSCA but not otherwise subject to notification requirements, so that EPA can monitor environmental releases.

All manufacturers, processors, and distributors of microorganisms subject to TSCA are reminded of the requirement to report any information on substantial risks under TSCA section 8(e).

EPA is considering initiating rulemaking that would exempt from PMN requirements inter-generic microorganisms used solely in contained systems and never intentionally released to the environment.

1. *Premanufacture notification requirements*—a. *Overview.* EPA has determined that any microorganisms that are subject to TSCA (described in Unit III.B), and that through deliberate human intervention contain genetic material from dissimilar source organisms, are "new" and therefore subject to PMN requirements of TSCA. This interpretation is effective as of the date of publication of this notice.

Organisms are considered dissimilar for the purposes of this policy if they are from different genera. In the case of chemically synthesized genes, the Agency will follow the same principle, as clarified below in Unit IV. Detailed guidance on how to determine if organisms are from different genera is also provided in Unit IV.

The agency is excluding certain inter-generic combinations from PMN requirements, i.e., those inter-generic combinations in which the genetic material added to the recipient microorganism consists only of well-characterized, non-coding regulatory regions (see Unit IV). The resulting microorganisms do not possess new combinations of traits but rather exhibit quantitative changes in preexisting traits.

EPA is leaving unanswered, for now, the question of whether microorganisms containing genetic material from other microorganisms in the same genus (i.e., products of deliberate intra-generic combinations) and those which are developed from a single source microorganism (e.g., products of undirected mutagenesis, microorganisms with deletions) should also be considered "new." In the future, it is possible that EPA will decide that such microorganisms are "new," but for now they are not subject to PMN requirements.

b. *Background.* For purposes of administering TSCA, EPA must decide what constitutes a "new" microorganism which is subject to PMN requirements. As mentioned in the introduction to the EPA portion of this notice, EPA originally proposed a "process-based" approach to determining whether a microorganism is new. This approach stated that a microorganism would be considered new if significant human intervention had been used in developing it. For example, microorganisms altered by certain techniques—such as recombinant DNA and cell fusion—were presumed to be new because they involved significant human intervention. The question of which other techniques should be considered to produced new microorganisms was left open and comments were solicited.

After reviewing the comments, EPA considered a number of alternative ways to define "new" microorganisms. These are described in the "Response to Comments" document available as background to this **Federal Register** notice. In choosing among the alternatives, EPA carefully considered the TSCA mandate to review "new" substances. The Agency also considered related issues, for example, how well the options approximated risk (there was uncertainty with all the options in this respect) and how readily they could be implemented and enforced.

c. *Rationale.* Having reviewed the TSCA section 5 PMN requirements, the PMN regulations, the public comments, and the current state of science regarding genetic engineering, EPA has concluded that microorganisms resulting from intentional, inter-generic combinations of genetic material, except those in which the transferred material is only a well-characterized, non-coding regulatory region, constitute new microorganisms for purposes of PMN reporting. The reasons for this are set forth below.

First, the Agency considered the regulatory precedents established in compiling the inventory of existing chemical substances under section 8(b) of TSCA. Any chemical substance not on this inventory is "new" under section 5(a) of TSCA and is therefore subject to PMN requirements. Naturally occurring substances and substances derived from nature with limited human intervention are not explicitly listed on the inventory but are considered implicitly to be on it, and thus are not "new" (see 40 CFR 710.4(b)). A more detailed explanation of the TSCA inventory and related issues is found in the December 84 notice at pages 50887–50888.

Second, the Agency evaluated these regulatory precedents in the light of scientific knowledge about genetic engineering and microorganisms found in nature. On this basis, EPA concluded that microorganisms found in nature and developed without any deliberate combination of genetic material are not new, because they occur naturally and are derived through limited human intervention. Furthermore, from a scientific standpoint, these microorganisms have a very low probability of exhibiting new combinations of traits. Therefore, the Agency considers that from a legal and scientific standpoint they must be considered naturally occurring (not new). Because such microorganisms are naturally occurring, they are, as explained above, implicitly listed on the TSCA chemical substances inventory and not subject to PMN requirements.

Third, where genetic material has been combined among source organisms from different genera (inter-generic), the resulting microorganisms should be considered "new" because of the degree of human intervention involved, the significant likelihood of creating new combinations of traits, and the greater uncertainty regarding the potential risks of such microorganisms. However, transfer of genetic material consisting solely of well-characterized, non-coding regulatory regions is a special case. Where only regulatory material is

transferred, no distinctly new combinations of traits are introduced; instead, existing traits in the receiving microorganisms are amplified or changed quantitatively. For this reason, EPA believes that microorganisms formed only through inter-generic transfer of well-characterized, non-coding regulatory regions should not be considered "new" under section 5 of TSCA. This is reflected in the definition of "inter-generic" found in Unit IV.A.

It is possible to argue that some microorganisms formed through intra-generic combinations are products of significant human intervention and may exhibit new combinations of traits, and therefore that they should also be considered new. However, the Agency at this time believes that it is appropriate to exclude such microorganisms form its definition of "new" because distinctly new combinations of traits are unlikely to occur through transfers of genetic material among closely related organisms, because transfers among closely related organisms are more likely to occur in nature, and because the current state of taxonomy with regard to species designations is sufficiently unstable that it makes it difficult to include such microorganisms in a definition of "new" (the rationale is found in Unit I.D.3.a). As explained previously, however, the Agency will continue to review the status of such microorganisms and may, in the future, determine that certain combinations among similar organisms should be considered new.

In summary, EPA considers microorganisms deliberately formed to contain genetic material from different genera to be new, except where only well-characterized, non-coding regulatory regions are transferred. Conversely, intra-generic and non-engineered microbes are considered naturally occurring. These conclusions are based on the TSCA section 5 mandate to review "new" substances, and they also reflect a number of scientific considerations. Among these are (1) the Agency's concern that microorganisms formed with genetic material from different genera warrant regulatory review, because of the inherent uncertainty about the characteristics and behavior of such microorganisms, (2) the observation that microorganisms from different genera are less likely to exchange genetic material in nature than microorganisms that are more closely related, (3) the regulatory precedent that significant human intervention creates new substances for purposes of PMN under TSCA section 5, and (4) the necessity of having a definition of "new" that can be readily interpreted and enforced given the current state of science. These scientific and legal issues are more fully described in Unit IV.A.

d. *How to comply with the PMN requirements for new microorganisms.* The following requirements apply to "new" microorganisms produced for uses subject to TSCA authority (see Unit III.B.1 and 3). Detailed criteria for determining whether a microbe meets the definition of "new" microorganism (i.e., whether it contains genetic material from organisms from different genera) may be found in Unit IV.A.

Certain PMN policies in this notice are immediately effective. As of the date of publication of this notice, microorganisms that are being manufactured or imported for any TSCA commercial purposes other than research and development (R&D) are subject to PMN requirements 90 days prior to manufacture or import. This requirement applies to both contained and environmental uses that have gone beyond R&D. The requirement is based on the current provisions of 40 CFR Part 720. The definition of R&D under these regulations is clarified in the **Federal Register** of April 22, 1986 (51 FR 15096).

In addition, new microorganisms that are being manufactured or imported for R&D that involves environmental release will have to be reported to EPA at least 90 days before such activities begin. This policy will be implemented through amendments to 40 CFR 720 (explained fully in Unit III.C.3); in the meantime, persons manufacturing or importing new microorganisms for R&D activities involving environmental release are expected to comply with this policy voluntarily.

EPA believes that there are no manufacturers who are presently beyond the research and development stage with new microorganisms subject to TSCA. However, if any companies are now engaged in such activities, they should contact EPA and determine whether a PMN is necessary. If a company in this position contacts EPA promptly, it will not be considered out of compliance with policy. Further information on TSCA PMN requirements may be obtained from the TSCA Assistance Office (address provided at the beginning of the EPA portion of this notice).

(1) *How to know if a microorganism is subject to PMN.* As stated above, all microorganisms containing deliberate combinations of genetic material from organisms from different genera are new and subject to PMN. An exception to this policy is an inter-generic combination in which the genetic material added to the recipient microorganism consists only of well-characterized, non-coding regulatory regions. Unit IV.A of this notice contains detailed guidance that manufacturers should use to determine if their microorganisms meet this definition.

Submitters should consult the Agency if they have any questions about how to determine if a microorganism contains genetic material from different genera.

(2) *PMN exemptions.* EPA considers it a priority to exempt from PMN requirements new microorganisms that can be shown to meet the findings for exemption under TSCA section 5(h)(4). Further information on exemptions the Agency is considering may be found in Unit III.C.6 of this notice.

(3) *Submitting the PMN.* EPA expects manufacturers and importers to contact EPA well in advance of PMN submission, to allow sufficient time for prenotice consultation. These consultations will help the Agency and the submitter anticipate potential problems and expedite the review.

Information regarding new microorganisms should not be submitted on the standard PMN form, as this form is not applicable to microbial products. Instead, EPA and the submitter will discuss the level and types of information appropriate for the notice during prenotice consultations. The general kinds of information EPA expects to see in most submissions for microorganisms are described in the next unit below.

(4) *What information to submit.* Section 5(d)(1)(A) of TSCA specifies the information PMN submitters must provide in their notices, including information on production, workplace exposure, and release. In addition, under section 5(d)(1)(B) submitters must provide all test data related to the health and environmental effects of the new chemical substance in their possession or control. For more information on PMN requirements, persons should consult EPA's PMN rule (40 CFR Part 720).

In general, information to assess a substance's potential risk should be developed in a step-wise fashion. PMN submitters should begin with published literature on the source organisms, then move through laboratory, microcosm, growth chamber, and/or greenhouse studies that simulate as closely as possible the conditions of the eventual use or environmental application.

The remainder of this unit describes the types of information EPA expects

submitters to provide in PMNs on new microorganisms.

(a) *Identifying the microorganism.* PMN submitters must provide information that identifies microorganisms well enough to be listed on the TSCA chemical substance inventory. If the identity and/or use of the microorganism are claimed as confidential business information by the submitter, the PMN must also include a generic description of these items so that the information can be published in the **Federal Register.** Confidential submissions will be considered incomplete unless this generic information is included (see 40 CFR 720.65, 720.85, and 720.87).

Once a new microorganism is actually manufactured or imported, it will be listed on the inventory and will be no longer subject to PMN requirements. (See 40 CFR 720.102 concerning submission of a Notice of Commencement of Manufacture or Import.) EPA proposed an approach to inventory listings in a background document to the December 84 notice. The Agency received very few comments on this document, but those who commented stated that a general method for listing all microbes does not seem possible at this time. The Agency agrees and therefore intends to list microorganisms on the inventory on a case-by-case basis while developing more general procedures for different classes of microorganisms, and gaining experience that will help in developing standard listings. For now, the inventory definition will usually include the genus and species designations of source organisms and of the microorganism being reported, and other relevant phenotypic information such as nutritional and substrate requirements, proteins expressed, primary characteristics for which the microbe was engineered, and characteristics that are a typical for the species.

To identify the microorganism, EPA is likely to require information on:

i. Source organisms (e.g., taxonomy, source, reproductive cycle, and capacity for genetic transfer).

ii. Methods used to manipulate source organisms genetically to obtain the resulting product (e.g., source and function of genetic material to be combined; description of methods for vector construction and introduction, fusion of cells, injection of DNA, etc.).

iii. The special functions obtained (e.g., new traits intended to be expressed; selection method; nature and amount of source genetic material remaining in the product microorganism; genetic stability of new trait).

(b) *Risk assessment information.* Data required for conducting the risk assessment will vary according to the specifics of each case, but in general will fall into several major categories: Information on exposure, environmental fate, and human health and environmental effects.

If the microorganisms will be produced in enclosed, commercial-scale facilities, or used solely in physically contained systems, the notice should include the following information:

i. Production processes (e.g., culture conditions and requirements; sites, methods, and amounts of manufacture, processing, storage, and shipment; volume, composition, and disposal of wastes).

ii. Workplace exposure and worker practices (e.g., potential for exposure, worker protection practices, and equipment).

iii. Containment and possible releases (e.g., potential sources and characteristics of releases, physical containment methods, emergency back-up systems, monitoring, and detection methods in event of a release).

In the case of small-scale field tests and other environmental releases, EPA expects that the submitter will provide information on:

(A) Purpose and intended effect of application.

(B) Site of application and surroundings, including geographic, physical, chemical, and biological features.

(C) Numbers of microorganisms and methods of application.

(D) Containment and mitigation measures (e.g., procedures in event of accidental release, for emergency termination of the application, and to reduce dispersal beyond the site).

(E) Monitoring (e.g., detection procedures including their limits, sampling procedures).

For field tests and other environmental releases, data on environmental fate and effects will be essential. In such cases, manufacturers should assume, in the absence of data to the contrary, that the microorganisms may present a risk because of their potential to reproduce and exhibit new traits. Therefore, EPA will expect manufacturers to provide test and other data demonstrating the microorganisms' safety. These data should include:

(i) General background information on the source organism (e.g., habitat and geographic distribution, interactions with other organisms, involvement in biological cycling processes, potential for genetic exchange in nature).

(ii) Test data on the new microorganism itself, indicating its potential for survival, replication, dissemination, and genetic exchange with other organisms.

For further guidance, manufacturers should refer to the "Proposed Points to Consider for Environmental Testing of Microorganisms" developed by the National Institutes of Health Recombinant DNA Advisory Committee Working Group on Release into the Environment (Ref. 11). This document is particularly useful in developing data and information for submissions on small-scale field tests. While some points in this document relate solely to recombinant DNA techniques, most of the considerations are relevant to environmental tests of microorganisms regardless of the techniques involved in their production.

In addition, the Agency has prepared a more detailed guidance document entitled "Points to Consider in the Preparation and Submission of PMNs for Microorganisms." This document provides guidance on both environmental and industrial applications of microorganisms and is available from the TSCA Assistance Office (see address at the beginning of this notice).

At least three other documents will be useful to submitters. These are the "EPA Pesticide Assessment Guidelines: Subdivision M—Biorational Pesticides" (Ref. 20), a National Science Foundation report titled "The Suitability and Applicability of Risk Assessment Methods for Environmental Applications of Biotechnology" (Ref. 3), and a report by the Cornell Ecosystems Research Center titled "Potential Impacts of Environmental Release of Biotechnology Products: Assessment, Regulation, and Research Needs (Ref. 9).

e. *The PMN review.* All reviews of microorganisms will follow established administrative steps that are the same for all substances subject to PMN review. First, within 5 days of receiving the PMN, EPA will issue an announcement in the **Federal Register** describing the submission. The anouncement will include information on the identity of the new microorganism, the type of use, occupational exposure, production volume, a summary of test data submitted in the notice, and the submitter's identity. It will have confidential business information deleted according to the manufacturer's instructions, although EPA will strongly encourage manufacturers to release as much information as possible. If identity and use are claimed confidential, the Agency will include a generic description provided by the submitter.

EPA will have 90 days to review the PMN (extendable to 180 days), during which time the microorganism cannot be manufactured or processed for purposes other than research and development. Within the review period, the Agency may take action under section 5(e) of TSCA to prohibit or limit the activities, pending receipt of more data, or under section 5(f) or 6 to prohibit or limit the activities if there is sufficient information to make an unreasonable risk finding. Alternatively, EPA may take no action. In this case, manufacture and use may begin without restriction.

(1) *Case-by-case assessments.* Because of the very recent development of genetically engineered microorganisms for environmental use, there is little direct experience for conducting risk assessments on environmental releases of engineered microorganisms. In the absence of such experience, the Agency will conduct case-by-case reviews by using information from various scientific disciplines and by directly considering the features of specific genetically engineered microorganisms and their uses.

Many existing risk assessment approaches that are used for non-engineered microorganisms will contribute to the analysis of risks of engineered microbes in the environment. Some of these will be adopted with few if any changes, while others will require modifications to address special problems.

EPA believes that standardized protocols and procedures should be gradually blended with the case-by-case approach. As experience is gained, increasingly detailed guidance on routine testing and procedures can and will be developed.

(2) *Use of experts.* Expert judgment will be critical in determining information needs, evaluating protocols for testing, and reviewing potential risks. Because of the range of expertise that may be required in any given case, EPA intends to supplement its staff expertise by using experts from other government agencies, academia, and other independent sources. Persons will be specifically chosen for their knowledge and experience with organisms and uses related to the PMN under review.

As announced in the December 84 notice (and further described in Unit I of this notice), EPA is forming a biotechnology Science Advisory Committee to provide scientific advice and promote consistent review procedures.

Many academic experts may have financial or contractual relationships with biotechnology companies. Using non-Agency experts to assist in PMN reviews may therefore raise two potentially sensitive issues: Conflicts of interest and access by non-Agency experts to confidential business information. To address these issues, the EPA Office of Toxic Substances has developed special procedures to ensure that scientists contributing to biotechnology PMN reviews will not have conflicts of interest, and will have the necessary access to CBI to review the PMN without compromising trade secrets or violating TSCA CBI procedures. A document describing these procedures will be placed in the public record for this policy statement.

(3) *Major parts of the review process.* As stated earlier, EPA expects persons developing biotechnology products to engage in prenotice consultations with the Agency. During these discussions, EPA and the consulting company can identify preliminary concerns by considering the source organisms and intended uses of the microorganism subject to PMN. Significant time may be saved later in the PMN process if these concerns are addressed before the PMN is submitted.

Once the PMN is submitted, EPA will develop hazard and exposure assessments based on information submitted in the PMN, other available information, and consultation with non-Agency experts. Reviewers will consider the types of issues and questions described here and in the various guidance documents on risk assessments for microorganisms. As appropriate, they may also consult with external scientific experts, and their analyses may be peer reviewed by the Agency's biotechnology Science Advisory Committee.

As a risk/benefit statute, TSCA requires that benefits be estimated and considered in judging whether the risk may be unreasonable. While the risk assessments are being developed, Agency economists will estimate the benefits of the product based on information from the submitter, independent economic research, and consultation with non-Agency experts.

Finally, EPA staff will prepare a summary of the risks and benefits to use in reaching regulatory decisions.

(4) *Public involvement in the review.* EPA will issue for publication a section 5(d)(2) notice after receipt of a PMN for a new microorganism. EPA will also maintain a copy of the PMN, from which CBI has been deleted, in the OTS Public Information Office at the address listed in Unit VI of the EPA notice. EPA will welcome comments from interested members of the public on the PMN. The public is generally given 30 days to comment on a PMN after publication of the section 5(d)(2) notice.

In addition to the normal procedures for public comment on PMNs, EPA intends that meetings of its biotechnology Science Advisory Committee will be open to the public, although certain portions of meetings may have to be closed to discuss CBI. EPA also intends to charter its committee to include representatives from the lay public. These features will help to ensure that the public has access to information about EPA biotechnology policies and decisions.

(5) *Possible regulatory decisions.* The Agency may come to one of three decisions at the conclusion of a particular PMN review: (a) There is sufficient information to determine that the risks are reasonable, (b) there is sufficient information to determine that the risks are unreasonable, or (c) there is insufficient information to make a reasoned evaluation of risk, and the substance may present an unreasonable risk or there may be significant or substantial exposure to it.

Where the first decision is made, the Agency will notify the PMN submitter that the manufacture and use may proceed without restriction. In any event, unless the Agency notifies the company to the contrary before the end of the 90-day review period (with a possible 90-day extension), the submitter may begin to manufacture and use the organism.

A decision that risks will be unreasonable leads to two regulatory options. The Agency may require measures to reduce the risks to an acceptable level as a condition of manufacture and use. Alternatively, the Agency may prohibit manufacture or use of the microorganism if there are no alternatives available or practical to reduce the risk sufficiently. Such actions can be taken under TSCA section 5(f).

If the information submitted with the PMN is insufficient for a reasoned evaluation, and EPA finds that the microorganism may present an unreasonable risk or that there may be significant or substantial human exposure to it, or substantial environmental release, EPA may, under TSCA section 5(e), limit or prohibit the manufacture or use of the microorganism until sufficient data are submitted to the Agency to evaluate the risks.

2. *Significant new uses of microorganisms*—a. *Overview.* EPA intends to supplement its PMN requirements by requiring persons to notify the Agency before they introduce

pathogenic microorganisms (including microorganisms containing genetic material from pathogens) into the environment. Notification will be required for new environmental applications of genetically engineered pathogens prior to their release in any amounts into the environment, while notification for nonengineered pathogens will be required at a somewhat later stage, prior to their introduction on more than 10 acres of land (or some equivalent measurement standard in cases where acreage is not applicable, e.g. aquatic uses). If a pathogen used for agricultural purposes is subject to USDA review, it will not be subject to this policy. Applicable definitions may be found in Unit IV.

EPA intends to implement these notification requirements through a significant new use rule (SNUR) under TSCA section 5(a)(2). The public will have the opportunity to comment on the proposed rule, including its scope and possible categories that could be excluded from coverage.

Until the rule is final, EPA expects persons introducing pathogens into the environment for non-agricultural new uses to report to EPA voluntarily. In the unlikely event that an imminent hazard would arise during this interim period, the Agency could use its authority under section 7 of TSCA to immediately limit or prohibit the manufacture, processing, distribution in commerce, use, or disposal of the hazardous product.

b. *SNUR background.* Section 5(a)(2) of TSCA (15 U.S.C. 2604(a)(2)) authorizes EPA to determine that a use of a chemical substance is a significant new use. The Agency must make this determination by rule, after consideration of all relevant factors, including those listed in section 5(a)(2). Once EPA determines that a use of a chemical substance is a significant new use, section 5(a)(1)(B) of TSCA requires persons to submit a notice to EPA at least 90 days before they manufacture, import, or process the substance for that use.

Persons subject to a SNUR must comply with most of the same notice requirements and regulatory procedures as submitters of PMNs under section 5(a) of TSCA. EPA's review procedures and regulatory authority are the same for SNUR notices as for PMNs. However, if EPA does not take action on a SNUR notice, section 5(g) of TSCA requires the Agency to explain in the **Federal Register** its reasons for not taking action. Procedures and requirements for PMN review are described above in Unit III.C.1.

c. *SNUR rationale.* As explained in the December 84 notice, EPA recognizes that any approach to defining "new" microorganisms, including the one described in Unit III.C.1, excludes some types of microorganisms from PMN review and therefore may not address some significant potential risks. EPA believes there is one currently identifiable category of microorganisms that is not being treated as "new" under TSCA at this time but that should be reviewed before environmental release. That category includes pathogens and microorganisms that contain genetic material from pathogens (henceforth, both are referred to collectively as "pathogens"). As explained in more detail in Unit I, the Agency believes it is necessary to review pathogens released to the environment because of their ability to cause disease in microbes, plants, animals, and humans.

EPA intends to take a slightly different regulatory approach with nonengineered pathogens. The Agency will not require SNUR reporting on the use of nonengineered pathogens until they are to be used on more than 10 acres of land, or some equivalent standard (to be determined) for uses where acreage is an inappropriate standard (e.g. aquatic or subterranean uses). The reason for this exception is explained in Unit I.D., "Rationale for Approach."

To avoid duplicative requirements with USDA, EPA will exclude pathogens used solely for agricultural purposes from the scope of its SNUR. USDA permits to use such microorganisms are mandatory, while EPA review would be discretionary because these are not "new" microorganisms. However, new environmental applications of pathogens for non-agricultural purposes will be subject to EPA review as significant new uses, and will in some cases also be subject to USDA oversight (if they are plant or animal pests under the USDA definition). In such cases, USDA's review will primarily be for the purpose of detecting potential adverse agricultural effects, while EPA's review will focus on the potential non-agricultural impacts. See Unit I.E for an explanation of how the agencies will work together to coordinate their review.

EPA is considering whether it should also include provisions in the SNUR requiring notification prior to small-scale releases or commercial uses of other categories of microorganisms besides pathogens. For example, some people have expressed concern over nonindigenous microorganisms, and others have expressed concern over microorganisms that degrade structural components of nature such as lignin and cellulose. Members of neither category are subject to PMN when the microorganisms involved are naturally occurring or intra-generic (not new), and they would not be subject to the provisions for pathogens described above. However, they may present certain risks because they are new to the environment in which they are used or because of their degradative capabilities. The literature contains much documentation of the adverse effects that have occasionally been caused by nonindigenous microorganisms such as the chestnut blight fungus and Dutch Elm disease fungus. There is, on the other hand, very little known about many degradative microorganisms and their potential for adverse effects. The Agency will request comments on these concerns when it issues its proposed SNUR.

d. *Guidelines for voluntary compliance.* The SNUR that EPA will propose will describe, in detail, the persons who will be subject to the rule and the microorganisms and activities for which significant new use reporting will be required. In the meantime, EPA strongly encourages persons who are planning to manufacture, import, or process pathogenic microorganisms for non-agricultural, new environmental uses, except those used solely for agricultural purposes, to report their activities to the Agency and to provide information similar to that required for a PMN for a new microorganism.

For purposes of voluntary reporting, persons may use the following definitions and assumptions. These guidelines may be changed in the proposed and final forms of the SNUR.

(1) *How to know if a use would be considered a significant new use.* For purposes of voluntary reporting, the Agency encourages people to be as comprehensive as possible and to consider that any new, non-agricultural release of a pathogen to the environment is appropriate to report. "Environmental release" is defined in Unit IV.D, this definition should be used in the interim until the SNUR is final. Cases that may not be entirely clear, e.g., use in waste water treatment plants and use in mines or oil wells, should be reported until the Agency provides further guidance.

Many microorganisms that are pathogens or that contain genetic material from pathogens are being used in the environment already. For example, specific naturally occurring pathogens are used for waste treatment purposes and are tested in non-contained experiments. These applications of these specific microorganisms cannot be considered

significant "new" uses because they are ongoing. Therefore, persons now using pathogens in environmental applications will not be expected to notify the Agency of such uses of these pathogens, except for informational purposes (see Unit III.C.4).

In developing the proposed and final rule, the Agency will have to determine exactly which types of uses should be considered significant new uses, taking into account that the purpose of the rule is to ensure the Agency has the opportunity to review releases of pathogens that could entail significant exposure or risk to the environment or the public. Considerations relating to the appropriate scope of the rule will be discussed in the proposed SNUR, and the public will be invited to comment.

(2) *How to know if a microorganism is a pathogen.* Unit IV.B of this notice contains the definition of "pathogen" that the Agency will use for purposes of administering TSCA and FIFRA, and provides guidance on how to determine if a microorganism is a pathogen.

(3) *How to know if a microorganism is genetically engineered.* As discussed in Unit III.C.2.c, EPA will not require nonengineered pathogens to be reported until they are used on more than 10 acres of land (or some equivalent standard, not yet determined, for uses where acreage is an inappropriate standard). For now, a pathogen should be considered nonengineered if there has been no deliberate attempt to promote genetic changes. Any human intervention beyond removal from the environment and selection for the desired variant populations should be considered to result in an engineered microorganism.

(4) *Submitting the significant new use notice.* Persons subject to the SNUR will have to notify the Agency at least 90 days prior to any new, non-agricultural use involving environmental release of engineered pathogens. The Agency will treat nonengineered pathogens slightly differently; producers of nonengineered pathogens will be subject to significant new use notification 90 days prior to new uses involving environmental applications on more than 10 acres of land. Significant new use notifications for microorganisms should contain the same general types of information as PMN submissions for microorganisms. In all cases, SNUR notice submitters should initiate prenotice consultations with EPA well in advance of the actual submission, to expedite the Agency's review of the notice.

e. *Significant new use notice review.* EPA reviews of significant new uses of microorganisms will be conducted in a fashion similar to PMN reviews of microorganisms. The review must be completed in 90 days, extendable for good cause to 180 days. In conducting the review, EPA will use Agency and non-Agency scientists selected for their expertise on issues relevant to the specific case.

The Agency recognizes that various environmental uses of different types of pathogens pose very different levels of potential risk to human health and the environment. For example, risks should generally be lower when pathogens are applied in areas distant from host organisms; the manufacturer has used nonpathogenic strains of a pathogenic species; transferred genes are for a trait not directly involved in pathogenicity; the pathogenic source organisms have very narrow host ranges; and pathogenic genes have been deleted.

Because it recognizes these variations in risk, the Agency expects to subject some pathogenic microorganisms to more rigorous regulatory oversight than others.

3. *Research and development (R&D) exemption*—a. *Overview.* TSCA section 5(h)(3) exempts from PMN and SNUR notification requirements chemical substances manufactured in small quantities solely for R&D. However, to ensure adequate review prior to environmental release, EPA intends to require persons developing "new" microorganisms and certain engineered pathogens to notify EPA prior to any research involving environmental release. This will be accomplished by amending the PMN rule (and possibly the general SNUR rules in 40 CFR Part 721) to specify that field testing of microorganisms does not fall within the definition of "small quantities" for R&D. Until the necessary rule changes implementing this policy are final, EPA expects submitters to comply with this policy voluntarily. Notice submitters are advised to consult the Agency if they are unsure whether a particular test is subject.

b. *Background.* As explained in the December 84 notice (at page 50891), section 5(h)(3) of TSCA exempts from PMN requirements new chemical substances produced "only in small quantities solely for purposes of research and development." ("Small quantities" must be defined by rule.) The same exemption applies to substances produced for significant new uses. if this exemption as now defined were applied to living microorganisms, many microorganisms would go unreviewed by EPA until perhaps years after their initial testing in the environment. Because microorganisms can reproduce in the environment and have the potential to exhibit new traits, this has raised the question of whether these field tests for R&D purposes could present significant risks that would go unreviewed.

Because of this concern, an important issue for EPA in implementing the biotechnology program has been whether to alter the R&D exemption of TSCA section 5 notice requirements in the case of living microorganisms. EPA requested and received substantial public comments on this issue, which it considered carefully in developing this policy. The comments and EPA's response to them are described in the EPA "Response to Comments" document, available as part of the public record of this EPA notice.

c. *Rationale.* The PMN rule definition of "small quantities" for R&D has been appropriate for most chemicals subject to TSCA because of the assumption that chemical R&D generally involves limited exposure and therefore limited risk. In the case of field tests involving living microorganisms, this assumption will not always apply. Microorganisms that survive may reproduce, potentially leading to significant exposure and risks. Because of their ability to reproduce and therefore increase beyond the amount originally released, living microorganisms used in the environment cannot be considered to meet the commonly understood meaning of "small quantities" for research and development, and thus do not qualify for the exemption.

d. *Implementation.* To implement the change in the R&D exemption, EPA intends to amend the PMN rule (40 CFR 720.3(cc) and 720.36) and possibly the SNUR general provisions in 40 CFR Part 720. The amendments will specify when a microorganism is considered not to qualify for the R&D exemption, and will provide enforceable standards for that determination.

Until the R&D rule amendments are final, EPA expects commercial researchers intending to release new, living microorganisms and engineered pathogens into the environment to report their activities to the Agency as explained in the units on PMN and SNUR notification (Units III.C.1 and 2). In addition, EPA strongly encourages researchers, prior to the time of reporting, to maintain records regarding containment procedures used in their experiments. Researchers should use the definition of "environmental release" provided in Unit IV.D as a guide, ask EPA for further guidance if questions arise, and in general be as inclusive as possible in their estimation of what should be reported.

e. *Noncommercial R&D.* Noncommerical R&D is exempt from section 5 of TSCA under section 5(g) and would therefore be exempt from PMN and SNUR requirements even under the proposed amendments. EPA has defined "noncommercial" for all chemical substances subject to TSCA section 5 in a final rule published in the **Federal Register** of April 22, 1986 (51 FR 15096). As a general guide, R&D done by a commercial company should be considered commercial, and purely academic R&D should be considered noncommercial. For more specific guidance, the reader should examine the definition of "noncommercial" in the final rule and the discussion of "noncommercial" in the proposed PMN rule revisions published in the **Federal Register** of December 27, 1984 (49 CFR 50208). Readers should also note that the NIH Recombinant DNA Advisory Committee (RAC) and USDA Agriculture Biotechnology Recombinant DNA Advisory Committee (ABRAC) have jurisdiction over many noncommercial R&D activities, specifically recombinant DNA experimentation at institutions that receive funds from NIH and USDA. Both of these committees encourage submission of experiments from other sources as well.

4. *General information reporting requirements*—a. *Overview.* EPA intends to collect general information prior to the environmental use of microorganisms that are subject to TSCA, but that are not the subject of premanufacture or significant new use notification requirements. EPA will gather such information by means of a section 8(a) reporting rule. The information EPA collects will primarily be used to monitor environmental uses of microorganisms, thus making the Agency aware of cases that may require special regulatory action under other TSCA authorities. It will also be used to help the Agency evaluate and modify the scope of its biotechnology programs over time.

b. *Section 8(a) background.* Section 8(a) of TSCA authorizes EPA to issue rules requiring manufacturers, importers and processors of specified chemical substances to submit information to the Agency. TSCA section 8(a)(2) authorizes the Agency to obtain a broad range of data, including information on chemical identity and structure, production, use, exposure, disposal, and health and environmental effects. Small manufacturers, importers, and processors, as defined by EPA, are exempt from section 8(a) reporting and recordkeeping requirements, with certain statutory exceptions.

c. *Rationale for section 8(a) rule.* As explained in the overview to the EPA portion of this notice, the biotechnology review procedures described in this notice are intended to focus on the current areas of highest priority based on considerations of risk and on determinations about what makes a microorganism "new." However, there is a relatively high degree of scientific uncertainty involved in establishing these priorities at this early stage in the development of the biotechnology industry. The Agency cannot say definitively that all the microorganisms and uses that are not at this time subject to notification requirements will never need to be regulated or should never be subject to notification requirements in the future.

EPA believes that TSCA section 8(a) is the best mechanism available for determining whether specific microorganisms or categories of microorganisms not subject to PMN or SNUR notice requirements may need to be regulated. The Agency must be aware of how microorganisms are being used in the environment to fulfill its responsibility to identify and prevent important or immediate hazards that might unexpectedly arise with specific uses. The section 8(a) reporting will also provide EPA with necessary information to assess whether its overall priorities with regard to biotechnology regulation have been, in fact, appropriately set and whether they should change over time. As was pointed out by many comments on the Agency's first proposed statement on biotechnology, flexibility and incorporation of new information should be major components of any regulatory scheme.

d. *Implementation*—(1) *Who will have to report under section 8(a)?* When promulgated, EPA intends for this rule to apply to manufacturers, importers, and processors of microorganisms that are subject to TSCA and to be released in the environment, but are not otherwise reviewed under the PMN and SNUR policies described earlier. In other words, general information will be required prior to environmental releases of all microorganisms that are subject to TSCA and that are non-engineered pathogens, or that are intra-generic or naturally occurring non-pathogens.

Although the rule will apply in general to the above groups, small manufacturers, importers, and processors are usually exempt from section 8(a) reporting and recordkeeping requirements. EPA has established general exemption standards for small manufacturers (40 CFR Part 704). The Agency will consider whether these standards should be retained or altered in some way to reflect considerations particular to the biotechnology industry.

When EPA issues its notice of proposed rulemaking, the public will have an opportunity to comment on the question of who will have to report under the rule.

(2) *What information will have to be reported under section 8(a)?* EPA is in the process of considering exactly what information it will propose to require on microbial products and uses under the section 8(a) reporting rule. In deciding what information should be reported on microorganisms, EPA will consider what information is necessary for the Agency to assess the safety of planned environmental releases, to evaluate its biotechnology regulations over time, and to consider necessary and appropriate improvements. The Agency will also consider the economic impact of special information and whether the information is generally "known to or reasonably ascertainable by" potential respondents to the rule.

5. *Reporting of information on substantial risks.* All manufacturers, processors, and distributors of microbial products subject to TSCA, including those involved in research and development, are reminded of their responsibility to notify EPA immediately of any new information which "reasonably supports the conclusion that such substance or mixture presents a substantial risk of injury to health or the environment" (TSCA section 8(e)).

Guidance on the section 8(e) requirement was published in the **Federal Register** of March 16, 1978 (43 FR 11110). Manufacturers, processors, and distributors will find that this policy statement provides general guidance on TSCA section 8(e) reporting, but it should not be considered exhaustive in terms of the types of information that would reasonably support a conclusion of substantial risk. Specifically with regard to microorganisms, the types of information that should be reported include but are not limited to (1) pathogenicity to humans, plants, animals, or microbes, (2) significant ability to displace other organisms in the intended use area, (3) significant potential to transfer genetic material to other organisms, and (4) any other significant potential to cause harm to human health or the environment.

Manufacturers, processors, and distributors should be vigilant and immediately report substantial risk information concerning microorganisms subject to TSCA.

6. *Exemptions from premanufacture notification requirements.* Section 5(h)(4) of TSCA allows EPA, by rule, to exempt from PMN requirements chemical substances that it finds will not present unreasonable risks. EPA expects to use this authority, where appropriate, to reduce the burden of PMN reporting requirements.

In its December 84 notice (at page 50891), EPA asked for comment on the issue of whether certain microorganisms or categories of microorganisms should be exempt from PMN requirements under the authority of section 5(h)(4) of TSCA. Ten respondents stated that microorganisms used in closed systems should be exempt under the 5(h)(4) provision, although several specifically remarked that appropriate biological and physical containment conditions should first be determined and met. Others suggested modifications to this approach, such as expedited reviews or reduced information requirements rather than outright exemption, or application of the exemption only to specific microorganisms or substances (e.g., *E. coli.* used in contained systems). One commenter stated that an exemption was not appropriate because there is no current Federal authority to determine safety in the event of accidental release.

Under TSCA, the PMN policy described in Unit III.C.1 extends to commercial-scale, closed system uses of microorganisms as well as environmental releases. The statute requires that all manufacturers of "new" substances must submit PMNs, regardless of whether they are used in contained facilities or open environments. Nonetheless, EPA believes that closed-system uses of new microorganisms will often present lower risks than environmental releases of the same organisms. The contained uses may therefore warrant a section 5(h)(4) exemption, and EPA is hereby announcing its intent to pursue that possibility.

Since the Agency does not yet have sufficient information to make the necessary finding under section 5(h)(4) that such activities "will not present an unreasonable risk of injury to human health or the environment," it is soliciting more data to support that finding in the case of closed system uses. The Agency would appreciate receiving data that would support an exemption either for all inter-generic microorganisms used in closed systems, or for specific categories of such microbes. For example, a category that has been suggested for exemption is inter-generic combinations involving microorganisms that exchange DNA by known physiologic processes, and that are on the NIH RAC exchanger list. This possible exclusion is mentioned in the OSTP preamble published in this **Federal Register.**

Information and data relevant to this issue should be sent to EPA at the address listed at the beginning of this notice.

In addition to supporting the use of section 5(h)(4) exemptions, the Agency will try to identify categories of microorganisms that pose lower risk even though they may not meet the necessary findings for exemption. In such cases, the Agency will consider reducing the burden of PMN reporting by lowering the information requirements associated with the PMN, and by conducting expedited reviews. The Agency requests any data or information that could be used to support exemptions or expedited reviews.

IV. Definitions of Terms for Regulatory Purposes

As explained in the previous units of this notice, EPA intends at this time to focus its regulatory programs on microorganisms containing genetic material from dissimilar source organisms (defined as organisms from different genera), pathogenic microorganisms, microorganisms containing genetic material from pathogens, nonindigenous microorganisms, and TSCA nonagricultural environmental applications. Applicable requirements are described in Units II and III of this notice. The purpose of this unit is to provide detailed information on how a person should determine whether a specific product is a pathogen, contains genetic material from a pathogen, contains genetic material from organisms of different genera (inter-generic combination), is nonindigenous, is released to the environment, or is used for nonagricultural TSCA purposes.

A. How To Determine if a Product Is an Inter-Generic Combination

For purposes of implementing its concept of "new" microorganisms, the Agency is defining "new" microorganisms as those formed by deliberate combinations of genetic material from organisms of different genera.

This standard is purposely based on the taxonomic designations of microorganisms. While imperfect in many ways, taxonomy appears to provide the best available standard for "dissimilarity" among organisms, for the following reasons:

1. Although subject to periodic revision within the scientific community, taxonomy is a common language used by scientists to describe how organisms are similar and dissimilar (Refs. 4, 18).

2. Taxonomy reflects the most recent scientific observations about phenotypic and genotypic differences between organisms.

3. Taxonomy provides a universally available point of reference that can be understood by industry and enforced by the Agency.

4. EPA expects microorganisms being used in biotechnology research and development will have or can be assigned clear taxonomic designations; therefore, the use of taxonomic standards imposes few if and additional requirements on industry.

5. There is a significant adminstrative advantage to independently established criteria such as taxonomic standards, because EPA will not have to create and maintain a separate set of criteria for regulatory purposes.

The Agency expects all manufacturers to know or determine the currently accepted designations (genus, species) of the source organisms they have used in producing microbial products subject to FIFRA and TSCA. In addition, EPA expects submitters to use taxonomic literature and taxonomic experts, if necessary, to determine the correct identity of their microorganisms. A number of commenters on the December 84 notice stated that organisms manipulated by modern genetic engineering will in most cases already be well characterized. This fact should make implementation of this policy relatively easy in most cases.

Excluded from this policy on inter-generic combinations are microorganisms that have resulted from the addition of inter-generic material that is well-characterized and contains only non-coding regulatory regions such as operators, promoters, origins of replication, terminators, and ribosome-binding regions.

"Well-characterized, non-coding regulatory regions" means that the producer of the microorganism can document the following:

a. The exact nucleotide base sequences of the regulatory region and any inserted flanking nucleotides.

b. The regulatory region and any inserted flanking nucleotides do not code for protein, peptide, or functional RNA molecules.

c. The regulatory region solely controls the activity of other regions that code for protein or peptide molecules or act as recognition sites for the initiation of nucleic acid or protein synthesis.

EPA emphasizes that this policy excludes only inter-generic combinations that have resulted solely from the addition of well-characterized, non-coding regulatory regions. If the final microorganism contains any regions from organisms of other genera that do not meet this restriction, such as coding regulatory regions or any poorly characterized regions, the microorganisms is considered new and does not come under the exclusion for regulatory regions discussed above.

To document these features, EPA expects that companies will use sources such as citations to published scientific literature, copies of unpublished studies relied upon, or data from tests performed to determine the above characteristics.

If persons do not know the genera of particular organisms, they should consult standard sources such as the following:

i. Bacteria

(1) Skerman, V.B.D., V. McGowan, and P.H.A. Sneath. 1980. Approved list of bacterial names. International Journal of Systematic Bacteriology 30:225–420.

(2) Moore, W.E.C., E.P. Cato, and L.V.H. Moore. 1985. Index of the bacterial and yeast nomenclature changes published in the International Journal of Systematic Bacteriology since the 1980 approved list of bacterial names (1 January 1980 to 1 January 1985). International Journal of Systematic Bacteriology 35:382–407.

Manufacturers should consult issues of the International Journal of Systematic Bacteriology for validly published names and for names placed on Validation Lists since January 1985.

ii. Algae

(1) DeToni, 1889. Sylloge Algarum.

(2) Index Kewensis. 1895-present. (Royal Botanical Gardens, Kew.)

iii. Protozoa

(1) Nomenclator Zoologicus. 1758-present. Published in four volumes and two supplements from 1939 onwards. Edited by S.A. Neave. Zoological Society, London.

(2) Index Zoologicus. 1800–1900. Charles Owen Waterhouse. (Published 1902.) Edited by David Sharpe. Zoological Society, London.

(3) Index Zoologicus. 1902-present. (Zoological Society, London.)

iv. Fungi

(1) Saccardo, P.A. 1882–1921. Sylloge Fungorum. (Pavia, 25 vol.)

(2) Clements, F.E. and C.L. Shear. 1931. The Genera of Fungi (H.W. Wilson and Co., N.Y.)

(3) Index to Fungi. 1940-present. Commonwealth Mycological Institute, Kew, Surrey, England.

(4) Petrak's List of Fungal Names. 1922–1940. Commonwealth Mycological Institute, Kew, Surrey, England.

(5) Hawksworth, D.L., B.C. Sutton, and G.C. Ainsworth. 1983. Ainsworth and Bisby's Dictionary of the Fungi. Commonwealth Mycological Institute, Kew, Surrey, England.

v. Viruses

(1) Mathews, R.E.F. 1979. Classification and nomenclature of viruses, 3rd report of the International Committee on Taxonomy of Viruses. Intervirology 12(3–5):1–199.

If the taxonomic positions of source organisms are ambiguous or if the boundaries of a genus are in dispute, the Agency expects the submitter to be aware of these controversies. Ambiguities at the species level or lower will not affect the FIFRA and TSCA policies. However, if the taxonomy at the genus level is controversial, such that organisms may be considered by some to belong to the same genus and by others to belong to different genera, the submitter must comply with the applicable requirements of FIFRA or TSCA, or come to EPA for a case-specific determination (address provided at the beginning of this notice). In general, submitters should expect that microorganisms will be considered inter-generic if the taxonomy of either source organism, at the genus level, is controversial.

In the case of chemically synthesized genes, the Agency will follow a similar principle. The genetic sequence of the synthesized gene may be identical to a sequence known to occur in an organism in the same genus as the recipient microorganism. If so, the resulting microorganism will be considered intra-generic. However, the producer should be prepared to document how it made this determination. Conversely, the sequence of the synthesized gene may be different or not known to be identical to a sequence in the genus of the recipient microorganism. In this case, the resulting product will be considered inter-generic.

EPA's definition of inter-generic combinations contains a standard of intent on the part of the manufacturer or producer. Inter-generic combinations that occur as unintentional byproducts of microorganisms coming in contact with one another will not be considered subject to the provisions of TSCA and FIFRA that apply to inter-generic combinations. For example, inter-generic combinations may occur at very low frequencies if microorganisms from different genera are applied to the same plot of land, or are sold together as mixtures. Similarly, if manufacturers develop microorganisms that are naturally infected with viruses, and if the developer did not intend to promote and did not provide conditions actively promoting the infection of the microorganisms with the naturally occurring viruses, then the microorganisms containing naturally occurring inter-generic combinations would not be considerd inter-generic under the FIFRA and TSCA policies.

On the other hand, if the manufacturer or producer intentionally provides conditions to promote genetic transfer, or if inter-generic microorganisms are primary components of a product or mixture, then the microorganisms will be considered inter-generic and subject to the applicable provisions of FIFRA and TSCA.

Submitters should consult the Agency if they have any questions about these distinctions.

B. How to Determine if a Product Is a Pathogen

For the purposes of this policy, a pathogen is defined as a virus or organism (including its viruses and plasmids, if any) that has the ability to cause disease in other living organisms (i.e., humans, animals, plants, or microorganisms). A disease is an abnormal physiological function in an organism, occurring as a consequence of the activity of proliferating microorganisms directly associated with or infecting the host organism, or due to biologically active substances such as toxins, antibiotics, or growth regulators produced by a microorganism (Refs. 5, 6, 7, 8, 14, 19).

This policy is not meant to include such organisms as competitors or colonizers of the same substrates, commensalistic or mutualistic microorganisms, or opportunistic pathogens. However, if a microorganism has more than one mechanism for affecting other organisms and one of these is pathogenicity, then the microorganism is considered to be a pathogen.

A microorganism will be subject to EPA policies regarding pathogens if:

1. The organism belongs to a pathogenic species or to a species containing pathogenic strains, according to sources identified by EPA below, or from information known to the producer that suggests that the organism is a pathogen; excepted are organisms belonging to a strain used for laboratory research or commercial purposes and generally recognized as non-pathogenic according to sources identified by EPA, or information known to the producer and EPA; an example of a nonpathogenic strain of a pathogenic species is *Escherichia coli* K–12; examples of nonpathogenic species are *Bacillus subtilis, Lactobacillus acidophilus,* and *Saccharomyces* species; or,

2. The organism has been derived from a pathogen or has been deliberately engineered such that it contains genetic material from a pathogenic organism as defined in item 1, above. An exception to this requirement is a genetically engineered organism developed by transferring well-characterized, non-coding regulatory regions from a pathogenic donor to a nonpathogenic recipient.

"Well-characterized, non-coding regulatory region" means that the producer of the microorganism can document the following:

a. The exact nucleotide base sequences of the regulatory region and any inserted flanking nucleotides.

b. The regulatory region and any inserted flanking nucleotides do not code for protein, peptide, or functional RNA molecules.

c. The regulatory region solely controls the activity of other regions that code for protein or peptide molecules or act as recognition sites for the initiation of nucleic acid or protein synthesis.

To document these items, EPA expects that companies will use sources such as citations to published scientific literature, copies of unpublished studies, or data from tests performed to determine the above characteristics.

The Agency is excluding genetically engineered organisms containing material from pathogens if the material transferred is from a pathogenic donor to a nonpathogenic recipient, and consists solely of well-characterized, non-coding regulatory regions. In this case, the transferred material does not code for traits directly associated with pathogenicity. The Agency believes that these organisms do not pose significant risks because they do not possess new combinations of traits or pathogenic traits, but instead exhibit quantitative changes in preexisting traits in a nonpathogenic recipient.

The Agency is excluding opportunistic pathogens for two reasons. First, in terms of risk priorities, outright pathogens are of significantly greater concern than organisms that would not act as pathogens except under unusual circumstances. Second, because of the very large number of microorganisms that could be considered to be opportunistic, their inclusion would result in an inappropriately restrictive policy.

There are a number of standard sources that can be used to determine whether a microorganism belongs to a pathogenic species. EPA is compiling a list of such sources, and is considering developing a list of pathogenic species, as part of future rulemaking activities. As interim guidance, persons should consider sources such as the following:

(1) Anne, W., ed. 1980. Fish Diseases. Springer-Verlag. New York.

(2) Anver, M.R. and C. Pond. 1984. Biology and Diseases of Amphibians. In Laboratory Animal Medicine, J.G. Fox, B.J. Cohen, F.M. Loew, eds. Academic Press, Orlando, FL.

(3) Bliss, D.E., ed. 1982–1985. Biology of Crustaceans (Volume 6 Pathobiology). Academic Press, New York.

(4) Blood, D.C., J.A. Henderson, and O.M. Radostits. 1979. Veterinary Medicine: A Textbook of the Diseases of Cattle, Sheep, Pigs, and Horses. 5th edition. Lea & Febiger, Philadelphia, PA.

(5) Braude, A. 1986. Medical Microbiology and Infectious Diseases. 2nd edition. W.B. Saunders, Philadelphia, PA.

(6) Buchanan, A.M. 1982. Veterinary Microbiology. Elsevier Scientific, Amsterdam.

(7) Buchanan, R.E. and N.E. Gibbons, eds. 1974. Bergey's Manual of Determinative Bacteriology. 8th edition. Williams and Wilkins Co., Baltimore.

(8) Cantwell, G.E., ed. Insect Diseases, M. Dekker, New York.

(9) Commonwealth Mycological Institute. Descriptions of Plant Pathogenic Bacteria, Fungi, and Viruses. Commonwealth Agricultural Bureaux, Kew, Surrey, England.

(10) Davidson, E., ed. 1981. Pathogenesis of Invertebrate Microbial Diseases. Allanheld, Osmum, Totowa, NJ.

(11) Ellis, A.E., ed. 1985. Fish and Shellfish Pathology. Academic Press, London.

(12) Gherna, R., W. Nierman, and P. Pienta, eds. 1985. Catalogue of Bacteria, Phages, rDNA Vectors. 16th edition. American Type Culture Collection, Rockville, Maryland.

(13) Hagan, W.A. and D.W. Bruner. 1981. Hagan and Bruner's Infectious Diseases of Domestic Animals: With Reference to Etiology, Pathogenicity, Immunity Epidemiology, Diagnosis and Bilogic Therapy. 7th edition. Comstock Publishing Associates, New York.

(14) Hitchner, S.B., ed. 1980. Isolation and Identification of Avian Pathogens. 2nd edition. American Association of Avian Pathologists, College Station TX.

(15) Jacobson, E. 1984. Biology and Diseases of Reptilgs. In Laboratory Animal Medicine, J.G. Fox, B.J. Cohen, F.M. Loew, eds, Academic Press, Orlando, Fl.

(16) Jong, S.C. and M.J. Gantt, eds. 1985. Catalogue of Fungi/Yeasts. 16th edition. American Type Culture Collection, Rockville, Maryland.

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The Agency expects that producers will be sufficiently familiar with the relevant literature and the species of the microorganisms under development that the pathogenicity or lack of it will already be known. Therefore, the Agency does not believe that determining whether a microorganism belongs to a pathogenic species based on published sources will be burdensome.

Where there is disagreement among sources about whether a strain belongs to a pathogenic species, the submitter must assume that it belongs to a pathogenic species, or come to EPA for a case-specific determination (address provided at the beginning of this notice).

As part of further rulemaking, the Agency plans to develop a list of nonpathogenic strains of pathogenic species, in addition to *E. coli* K–12, that will be exempt from Agency policies for pathogenic microorganisms. In the interim, if a submitter is using a strain that belongs to a pathogenic species, except *E. coli* K–12, the submitter should assume that it is pathogenic.

Because of the pathogenic potential of most, if not all, viruses, and because the species concept does not generally apply in virus taxonomy, the Agency will consider any product that is or contains genetic material from a virus to be a pathogen.

The Agency intends to update this guidance periodically, particularly the list of publications.

C. How To Determine if a Product Is a Nonindigenous Microorganism

A microorganism will be considered nonindigenous to any one of the geographic areas listed below if it is isolated from outside that area:

1. The continental United States, including Alaska, and the immediately adjoining countries (i.e., Canada and Mexico).

2. The Hawaiian Islands.

3. The Caribbean Islands including Puerto Rico and the U.S. Virgin Islands.

For example, a microorganism from Hawaii, developed for use as a microbial pesticide in the continental U.S., will be considered to be nonindigenous to the continental United States. Under FIFRA, the Agency would therefore be notified before initiation of small-scale field testing of the microbial pesticide in the continental U.S.

In normal usage, nonindigenous organisms are generally considered to be naturally occurring organisms placed in environments where they are not native or have not evolved. This concept means that a microorganism could be considered nonindigenous to an ecosystem that is adjacent to the one in which it evolved, nonindigenous to ecosystems far removed, or even indigenous to nearby or far-removed ecosystems. This happens for a number of reasons such as the widely varying effects of geographic barriers as isolating mechanisms; microbial dispersal mechanisms; and the biological, chemical, and physical features shaping different environments. Given the complexity and impracticality of determining whether a particular microorganism is indigenous to a wide range of habitats that may exist within regions and states, the Agency has selected continental boundaries to describe geographic regions that are clearly isolated and are easily used for administrative purposes. These boundaries will be used to determine whether a microorganism is nonindigenous and hence subject to particular provisions under FIFRA (see Unit II).

D. How To Determine if a Product Is Released to the Environment

In the future, it is likely that a definition of environmental release will be developed. In the interim, the Agency's approach will focus on when a microorganism is considered to be contained rather than when it is released.

A microorganism will be considered environmentally contained if the microorganism is used in a laboratory that complies with NIH RAC guidelines; or the microorganism is used in a contained greenhouse, fermenter, or other contained structure. In general, "contained greenhouse, fermenter, or other contained structure" means a building or structure that has a roof and walls. It should also have a ventilation system to minimize microbial release to the outdoors, a system for sterilizing water runoff and wastes, and a system for restricting insects, if any of these are plausible routes for dissemination of microorganisms. Experimenters should control pests, sterilize soil or other material containing microorganisms before disposal or reuse, and generally limit access only to those persons who must have access for research purposes.

E. How to Determine if a Product Is Used for Nonagricultural Purposes

An agricultural use of a microorganism is any use or application, the primary purpose of which is to produce, enhance, or cultivate plants or animals. The definition is not meant to include pesticides.

F. Definition of Plants and Animals

For the purposes of this EPA notice, plants are defined as multicellular organisms characterized by eukaryotic cell walls, photosynthetic ability, and embryonic development. Members include mosses, liverworts, and vascular plants (including most terrestrial crop plants). Animals are defined as multicellular organisms composed of eukaryotic cells with ingestive nutrition and lacking rigid cell walls and photosynthetic ability. Members include coelenterates, flatworms, molluscs, segmented worms, arthropods, echinoderms, and vertebrates.

V. References

The following books, articles, and reports were used in preparing this notice:

(1) Agrios, G.N. 1978. Plant pathology. Academic Press, New York, NY.

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VI. Public Record

EPA has established a public record for this statement of policy (docket number OPTS–00049A) which is available to the public in the OTS Public Information Office, 8 a.m. to 4 p.m., Monday through Friday, except legal holidays.

The Public Information Office is located in Rm E–107, 401 M St. S.W.,

Washington, D.C. 20460. The record includes all information considered by EPA in formulating this policy. The record includes the following categories of information:

1. **Federal Register** notices.
2. Support documents and reports.
3. Public comments, summaries of comments, and EPA's responses to comments on the EPA December 1984 Notice on biotechnology (49 FR 50860).
4. Communications.

The record also includes, by reference, published literature cited in this policy statement and generally available.

The docket of the record detailing its specific contents is available in the OTS Reading Room.

VII. Regulatory Assessment Requirements

A. Regulatory Flexibility Act

As required by the Regulatory Flexibility Act (5 U.S.C. 605(b)), EPA has assessed the impact of the immediately effective aspects of this policy on small businesses. EPA has determined that the immediately effective requirements will not create additional impacts on small businesses over those already identified in the final PMN rule, 40 CFR Part 720, and the Interim Policy for small-scale field testing of microbial pesticides (49 FR 40659).

B. Paperwork Reduction Act

The information collection requirements contained in this policy have been approved by the Office of Management and Budget (OMB) under provisions of the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 et seq. and have been assigned OMB control numbers 2070–0012 and 2070–0069.

DEPARTMENT OF AGRICULTURE

Final Policy Statement for Research and Regulation of Biotechnology Processes and Products

AGENCY: Department of Agriculture.

ACTION: Final policy statement.

SUMMARY: This statement presents, in final form, an explanation of the U.S. Department of Agriculture (USDA) policy for research and regulation of biotechnology applications in agrilculture and forestry. New Information is provided about policy for agricultural biotechnology research, proposed regulations, and scientific review mechanisms. The document also contains responses to comments and clarifications of the USDA policy statement published in the **Federal Register** on December 31, 1984 (49 FR 50897-50904).

FOR FURTHER INFORMATION CONTACT: For regulatory activities, contact Dr. James W. Glosser, Associate Administrator, Animal and Plant Health Inspection Service (APHIS), USDA, Room 313–E Administration Building, 12th and Independence Avenue, SW., Washington, DC 20250, telephone Area Code (202) 447–3580. For research activities, contact Dr. John Patrick Jordan, Administrator, Cooperative State Research Service (CSRS) USDA, Room 304–A, Administration Building, 12th and Independence Avenue, SW., Washington, DC 20250, telephone Area Code (202) 447–4423.

All written documents received by USDA on this notice are available for public inspection in Room 313–E Administration Building, 12th and Independence Avenue, SW., Washington, DC, weekdays between 8:00 a.m. and 4:00 p.m.

Table of Contents

I. Introduction

The USDA portion of the "Proposal for a Coordinated Framework for Regulation of Biotechnology" (hereafter referred to as the December 31, 1984 Notice) appeared at 49 FR 50897–50904. As a part of its policy perspective, USDA stated that agriculture and forestry products developed by biotechnology will not differ fundamentally from conventional products and that the existing regulatory framework is adequate to regulate biotechnology.

USDA has both research and regulatory responsibilities for biotechnology activities. This document provides significant new information in both areas. Section II describes 1985 **Federal Register** notices concerning USDA policies and responsibilities for biotechnology. Included in this discussion is an explanation of the assignment of responsibilities within USDA for the oversight of USDA funded research and for the regulation of the products of biotechnology. An understanding of the way in which USDA has divided these responsibilities should prove helpful to those in the private sector seeking review and/or approval of biotechnology applications.

A new section III has been added describing USDA's policy for agricultural biotechnology research. USDA is publishing as a companion document, USDA Guidelines for Biotechnology Research that will closely parallel the NIH Guidelines. The USDA guidelines will be issued under the authority of the Food Security Act of 1985 (Pub. L. 99–198). This Act amended section 1404(2) of the National Agriculture Research, Extension, and Teaching Policy Act (NARETPA). The Amendment gave the Secretary of Agriculture responsibility for establishing "appropriate controls with respect to the development and use of the application of biotechnology to agriculture." All USDA funded agriculture biotechnology research or research conducted at an entity receiving USDA funds would be subject to the USDA Guidelines for Biotechnology Research unless the specific research project is supported by and subject to the guidelines or regulations of another Federal agency. These Guidelines would encompass all phases of agricultural biotechnology research, i.e. (1) Contained laboratory experiments; (2) specialized isolation research (e.g., greenhouse, biotron); and (3) environmental research release (e.g., controlled and segregated field plots). USDA hopes that entities not required to comply with the Guidelines would voluntarily adhere to the requirements. To encourage compliance, USDA proposes to adopt the NIH policy of providing the researchers not required to comply with these Guidelines the opportunity to have their new biotechnology research proposals reviewed by USDA.

Those entities covered by the USDA Guidelines for Biotechnology Research would also be required to comply with any applicable statutes such as those set forth in section IV of this document, and any regulatory issues thereunder.

The Secretary of Agriculture has established an Office of Agriculture Biotechnology (OAB), which will have primary responsibility for implementing and coordinating the Department's policies and procedures pertaining to all facets of biotechnology. This includes the conduct of laboratory and field research, exprimentation on biotechnology products prior to their commercialization, and all matters of oversight of biotechnology in agriculture. The new office will report to the Assistant Secretary for Science and Education through the authority provided in the amendment to the Food Security Act of 1985. The Assistant Secretary for Science and Education will seek to establish an Agriculture Biotechnology Recombinant DNA

Advisory Committee (ABRAC) and shall continue the responsibilities for agriculture formerly handled by the NIH-RAC during the last 10 years. The OAB shall operate in a close parallel manner to the Office of Recombinant DNA Activities (ORDA) of the National Institutes of Health. This includes the responsibility of the ABRAC and the implementation of the USDA Guidelines for Biotechnology Research. The NIH system is well respected both domestically and worldwide, and has achieved a high degree of efficiency in achieving broad confidence in the safety of new biological research conducted under its requirements.

The OAB also will serve as a focal point for coordinating a National Biological Impact Assessment Program, which is to evaluate and monitor the potential impacts of biotechnological processes and products on safety and the environment.

Section IV contains USDA's regulatory policy statements for veterinary biological products, plants and plant products, meat and poultry products, and seeds. USDA stated in the December 31, 1984 Notice that while its existing regulatory framework is adequate, it would constantly reevaluate its regulatory position and should additional regulatory measures become necessary, amend its regulations (49 FR 50904). For veterinary biologicals regulated under the Virus-Serum-Toxin Act (VSTA), USDA has identified three categories which may be derived by recombinant DNA techniques or developed from hybridomas. The categories are based on biological characteristics and safety concerns, and are described fully in section IV(A). The first category consists of inactivated recombinant DNA-derived vaccines, bacterins, bacterin-toxoids, virus subunits, or bacterial subunits, as well as monoclonal products. This category presents no new or unusual safety or environmental concerns. The second category includes those products containing live microorganisms that have been modified by the addition or deletion of one or more genes. Such products will be evaluated under current regulatory policies and procedures to assure that the addition or deletion of specific genetic information does not impart increased virulence, pathogenicity, or survival advantages. The third category includes products using live vectors to carry recombinant derived foreign genes for immunizing antigens and/or other immune stimulants. Characteristics of safety and transmission must be established fully before questions and concerns dealing with safety to humans, animals, and release into the environment can be answered and before such products can be considered for licensing. Section IV(A) also includes new information about revised USDA review procedures for the importation of cell cultures and hybridomas. A brief discussion is included about the proposed regulations implementing the provisions of the amendments to the VSTA contained in the Food Security Act of 1985.

For organisms and products derived by the techniques of genetic engineering, USDA is proposing new rules to regulate organisms which are plant pests or which there is reason to believe are plant pests. It is USDA's policy to regulate certain genetically engineered organisms if the donor, vector/vector agent, or recipient organism is a member of a group of organisms that are known to contain plant pests, or if based on experience, USDA determines that a genetically engineered organism or product is a plant pest or if USDA has reason to believe that a genetically engineered organism or product is a plant pest. The proposed regulations are summarized in section IV(B).

The USDA policy for regulating meat and poultry products and seeds derived through biotechnology remains substantially as stated in the December 31, 1984 Notice, and appears in section IV (C) and (D).

A new section (V) has been added describing the scientific review mechanisms to be established by USDA to assist USDA Agencies in biotechnology research and regulatory decision-making. USDA has established a Committee on Biotechnology in Agriculture (CBA) chaired by the Assistant Secretary for Science and Education and the Assistant Secretary for Marketing and Inspection Services.

A detailed summary of comments on the December 31, 1984 Notice and USDA responses appears as section VI. The comments are organized to conform to the form of the December 31, 1984 Notice, with general comments and responses on the USDA regulatory philosophy followed by comments and responses on specific aspects of USDA's regulatory structure.

II. Notices

Three **Federal Register** notices concerning the Department's biotechnology related activities have been published subsequent to publication of the December 31, 1984 Notice.

On July 19, 1985, a document amending the delegations of authority of USDA to assign responsibility for these research and regulatory activities (7 CFR Part 2) was published in the **Federal Register** (50 FR 29367-29368).

In this document, the Secretary of Agriculture delegated responsibility to the Assistant Secretary for Marketing and Inspection Services to coordinate the development and carrying out of all matters and functions pertaining to the Department's regulation of biotechnology and to act as liaison on all matters and functions pertaining to the regulation of biotechnology between agencies within the Department and between the Department and governmental and private organizations. These responsibilities were further delegated from the Assistant Secretary for Marketing and Inspection Services to the Administrator of the Animal and Plant Health Inspection Service (APHIS).

Also in this document, the Secretary of Agriculture delegated responsibility to the Assistant Secretary for Science and Education to coordinate the development and carrying out of all matters and functions pertaining to agricultural research involving biotechnology conducted or funded by the Department including the development and implementation of guidelines for oversight of research activities, and to act as liaison on all matters and functions pertaining to agricultural research in biotechnology between agencies within the Department and between the Department and other governmental, educational and private organizations.[1]

On September 23, 1985, USDA's APHIS published a notice which contained its policy statement and requirements for the control and protection of documents that contain confidential business information concerning biotechnology and the veterinary biologics program (50 FR 38561-38563).

On November 14, 1985, the Office of Science and Technology Policy published a notice in the **Federal Register** announcing the establishment of the Biotechnology Science

[1] The Assistant Secretary for Science and Education oversees the research activities of the Agricultural Research Service (ARS), the Cooperative State Research Service (CSRS), the Extension Service (ES), and the Office of Grants and Program Systems (OGPS). The Assistant Secretary for Marketing and Inspection Services oversees the regulatory activities of the Animal and Plant Health Inspection Service (APHIS), which includes Veterinary Services (VS) and Plant Protection and Quarantine (PPQ); the Agricultural Marketing Service (AMS); and the Food Safety and Inspection Service (FSIS). The policies and procedures of these agencies for biotechnology were described in the USDA portion of the coordinated policy statement at 49 FR 50899-50904

Coordinating Committee (BSCC) (50 FR 47174–47195). This Committee is to serve as an interagency forum for coordinating science issues related to research and commercial applications of biotechnology. The notice also stated that USDA will establish a Committee on Biotechnology in Agriculture (CBA) to assist in assuring that research and regulatory decisions are based on the best science available.

III. USDA Research Policy Statement

USDA supports research to promote and protect the general health and welfare of the people of the United States.[2] Research program include: Studies on production of food and agricultural processing and marketing; identity and development of new crop and animal sources of food, fiber, and energy; increased agricultural efficiency and reduction of dependence on petroleum-based products; development of improved management and conservation of soil, water, forest, and range resources. The programs are fulfilled through State, Federal, and private industry cooperative efforts.

In the areas of agricultural research relevant to biotechnology, many plant, animal, and microbial alterations have been developed for release through traditional genetic approaches such as mutagenesis and hybridization. In a complementary vein, beneficial introduction of organisms from abroad have established a sound base for research and regulatory oversight. The experience with these bases provide a substantial knowledge base for conducting evaluations of the safety and efficacy of biotechnology processes and products.

USDA will evaluate the environmental impacts in the context of individual experiments that encompass the entire range of experimentation from contained facilities to open field testing. As knowledge and experience are gained, broadly applicable procedures and guidelines will be developed. Particular consideration will be given to the stability of engineered changes and the possibility that genetic elements might be transferred from one organism to another. Also important will be the development of data that will enable predictions of which organisms may become established in new ecosystems, and resulting environmental consequences.

USDA considers products developed through biotechnological techniques as no different from those products resulting from research using conventional techniques providing appropriate research review is conducted with established protocols. Agricultural biotechnology research activities require appropriate review to avoid untoward effects on human health and the environment.

USDA expects to rely on the existing network of scientific expertise in the agriculture research community. Thousands of plant selections, animal breeding lines, and microorganisms are tested annually at sites under varying climatic conditions through the Nation. This network of scientific expertise permits continual, open assessment of agricultural research and products of that research in the field. USDA has broad statutory authority to conduct and support research in wide ranging areas of agriculture. In addition to the authorities described in the matrix of Federal Laws related to biotechnology found in the **Federal Register** Notice of November 14, 1985 (50 FR 47174–47195) the Food Security Act of 1985 (Section 1404(2) of the National Agriculture Research, Extension, and Teaching Policy Act Amendments of 1985, Pub. L. No. 99–198), made the Secretary of Agriculture responsible for establishing "appropriate controls with respect to the development and use of the application of biotechnology to agriculture." Through this authority, and pursuant to the Delegation of Authority Pertaining to Biotechnology published in the **Federal Register** on July 19, 1985 (50 FR 29367–68), the Assistant Secretary for Science and Education will complete development of a national system of agricultural biotechnology research oversight in much the same manner that agriculture has been a part for the last 10 years through the NIH–RAC.

The Assistant Secretary for Science and Education has initiated the establishment of the Agriculture Biotechnology and Recombinant DNA Advisory Committee (ABRAC), to be managed through an Office of Agriculture Biotechnology (OAB) which is a parallel to the National Institutes of Health Recombinant DNA Advisory Committee (NIT–RAC) and Office of Recombinant DNA Activities (ORDA). The OAB will serve as the focal point for developing and coordinating USDA policies and activities pertaining to biotechnology research and will perform related interagency and public liaison functions. OAB will also assist in carrying out the responsibilities assigned to the Assistant Secretary for Science and Education, including the development and implementation of policies and procedures, and guidelines for the conduct of laboratory and field research.

All federally-funded agriculture biotechnology research or reseach conducted at an entity receiving USDA funds will be subject to the USDA Guidelines for Biotechnology Research, which are published as a companion document to this policy statement, unless the specific research project is supported by and subject to the guidelines or regulations of another Federal agency. These Guidelines encompass the entire spectrum of degrees of containment in agricultural biotechnology research i.e.: (1) Contained laboratory experiments; (2) specialized isolation research (e.g., greenhouse, biotron); and (3) environmental research agricultural biotechnology release (e.g., controlled and segregated field plots). Research investigators not required to comply with USDA Guidelines will be encouraged to follow these Guidelines. To assure consistency, USDA adopted the model established by the NIH of providing such researchers with the opportunity to have their biotechnology research proposals reviewed as required by the Guidelines.

The USDA Guidelines for Biotechnology Research require that research organization use the Institutional Biosafety Committee (IBC) concept as established by NIH. This requirement assures that each research organization and its investigators employ a multidisciplinary team to assist in carrying out their responsibilities under the Guidelines. The IBC's, as described in the Guidelines, would consist of persons with relevant agricultural expertise in areas such as recombinant DNA technology, biological safety, physical containment, and ecology. Requests for review beyond IBC should be sent to the Office of Agriculture Biotechnology (OAB) through the Assistant Secretary of Science and Education, Room 324–A, Administration Bldg., Washington, D.C. 20250.

These Guidelines also would require compliance with existing statutes of the USDA involving the movement of regulated organisms that require the issuance of a permit. The movement of microorganism injurious to plants and animals as well as the movement of certain non-indigenous plants and animals would continue to follow long-established procedures for USDA approval. After review, a permit, if needed, may be issued that allows movement. It is the responsibility of the research scientists to obtain that permit.

[2] See Addendum for Research Legislative Authorities.

The Assistant Secretary for Science and Education will complete establishment of a National Biological Impact Assessment Program (NBIAP) as indicated in the USDA Guidelines for Biotechnology Research. NBIAP would serve to assist USDA in the evaluation and monitoring of biotechnology research and impact over time. Coordination of NBIAP will be provided through OAB.

IV. USDA Regulatory Policy Statements

The existing USDA regulatory authority for biotechnology was listed in the matrix of the December 31, 1984 Notice at 49 FR 50860–50874 and described in brief at 49 FR 50898–50899. The statutes considered most applicable to biotechnology applications are the Virus-Serum-Toxin Act (VSTA) of 1913 (21 U.S.C. 151–158), the Federal Plant Pest Act (FPPA) of May 23, 1957 (7 U.S.C. 150aa–150jj), the Plant Quarantine Act (PQA) of August 20, 1912 (7 U.S.C. 151–164, 166, 167), the Organic Act of September 21, 1944 (7 U.S.C. 147a), the Federal Noxious Weed Act (FNWA) of 1974 (7 U.S.C. 2801 *et seq.*), the Federal Seed Act (FSA) (7 U.S.C. 551 *et seq.*), the Plant Variety Protection Act (PVPA) (7 U.S.C. 2321 *et seq.*), the Federal Meat Inspection Act (FMIA) (21 U.S.C. 601 *et seq.*), and the Poultry Products Inspection Act (PPIA) (21 U.S.C. 451 *et seq.*).

A. Veterinary Biological Products

Under the Virus-Serum-Toxin Act of 1913, 21 U.S.C. 151–158, the USDA exercises regulatory authority over all veterinary biologics imported into the United States or shipped or delivered for shipment interstate. Recent amendments contained in the Food Security Act of 1985 have extended this authority to products which are shipped intrastate or exported, and have given the Department additional enforcement mechanisms such as the power to detain and seize products. Under the VSTA, veterinary biologics may not be shipped or delivered for shipment if they are worthless, contaminated, dangerous, or harmful. Veterinary biological products must be prepared in a USDA-licensed establishment under regulations promulgated by the Secretary of Agriculture. Those products which are imported into the United States must be imported under a permit issued by the Secretary. The pertinent regulations for veterinary biologics are found in Title 9 of the Code of Federal Regulations, Parts 101 through 117. New regulations will be drafted to implement the provisions of the amendments to the VSTA. Such regulations will provide for a more comprehensive regulatory scheme, including seizure and condemnation and detention procedures. They also will establish procedures to be used in the issuance of special licenses and exemptions provided for by the legislative amendments.

Veterinary biological products are defined in the governing regulations, 9 CFR 101.2(w) as "all viruses, serums, toxins, and analogous products of natural or synthetic origin, such as diagnostics, antitoxins, vaccines, live microorganisms, killed microorganisms, and the antigenic or immunizing components of microorganisms intended for use in the diagnosis, treatment, or prevention of diseases of animals."

Licensing provisions for veterinary biological products and establishments are found in Part 102 of the USDA regulations (9 CFR Part 102). A product license requires the satisfactory completion of various requirements to assure purity, safety, potency, and efficacy of the products. The specific requirements were discussed in the December 31, 1984 Notice at 49 FR 50899.

Pursuant to § 103.3 (a) through (g) of the USDA regulations, a person may be authorized to ship unlicensed biological products for the purpose of evaluating experimental products by treating limited numbers of domestic animals if USDA determines that the conditions under which the experiment is to be conducted are adequate to prevent spread of disease and approves the procedures set forth in the request for such authorization (9 CFR 103.3 (a)–(g)).

Upon satisfactory completion of all requirements, including review and acceptance of labels, a U.S. Veterinary Biological Product License may be issued.

The application of new biotechnological procedures for the production of veterinary biological products is expanding constantly. For the purposes of licensing, biologics derived by recombinant DNA-techniques or developed from hybridomas, may be classified into three broad categories. This division is based upon the biological characteristics of the new products and the safety concerns they present, and is wholly analogous to the approach used in other veterinary biologics.

The first category includes inactivated recombinant DNA-derived vaccines, bacterins, bacterin-toxoids, virus subunits, or bacterial subunits. These nonviable or killed products pose no risk to the environment and present no new or unusual safety concerns. Monoclonal antibody (hybridoma) products used prophylactically, therapeutically, or as components of diagnostic kits also are included in this category.

The second category includes those products containing live microorganisms that have been modified by the addition or deletion of one or more genes. Deleted genes may code for virulence, oncogenicity, enzyme activity, or other biochemical functions. Added genes may result in the expression of new immunizing antigens or the production of novel biochemical byproducts such as beta-galactosidase. Precautions must be exercised to assure that this addition or deletion of specific genetic information does not impart increased virulence, pathogenicity, or survival advantages in these organisms which are greater than those found in natural or wild-type forms.

Modifications also must not impart undesirable new or increased adherence or invasion factors, colonization properties, or intrahost survival factors. It is important that genes added or deleted do not compromise the safety characteristics of the organisms. In most cases it is expected that they will be improved, and would therefore not pose any new threat to humans, other animal species, or to the environment.

The genetic information to be added or deleted must consist of well-characterized DNA segments. Required licensing data may include base pair analysis, sequence information, restriction endonuclease sites, as well as phenotypic characterization of the altered organism. A comparison is also required to be made between the genetically engineered organism and the wild-type form with respect to biochemical pathways, virulence traits, or other factors affecting pathogenicity.

The third category includes products using live vectors to carry recombinant-derived foreign genes that code for immunizing antigens and/or other immune stimulants. Live vectors may carry multiple recombinant-derived foreign genes since they can carry large quantities of new genetic information. They also are efficient at infecting and immunizing target animal species. These properties, for example, make vaccinia virus recombinants very popular subjects for vaccine development programs.

Live vectors currently being evaluated by licensees, applicants, and other research organizations include vaccinia, bovine papilloma virus, adenoviruses, Simian Virus–40, and yeasts. Characteristics of safety and transmission must be examined before questions and concerns dealing with

safety to humans, animals, and release into the environment can be answered and before such products can be considered for licensing.

USDA will continue to avail itself of additional expertise from the Public Health Service "Interagency Group to Monitor Vaccine Development, Production, and Usage." This interagency committee will be utilized to consider potential human health hazards from the use of veterinary biological products and to review issues such as those arising from the potential effect of organisms potentially pathogenic to people or animals.

Veterinary biological products prepared using modern biotechnological procedures such as recombinant DNA, chemical synthesis, or hybridoma technology will be treated similarly to products prepared by conventional techniques. The unlimited number and kind of products that may result from these modern biotechnology procedures make it impossible to define all requirements in specific terms. Each product is evaluated individually to determine what will be necessary to establish its purity, safety, potency, and efficacy. Scientific considerations may dictate generic areas of concerns or the use of certain tests for specific situations. Special assays, preferably using in vitro methods, may be required for potency and stability determinations. Additional tests may be required to assure safety, especially when live microorganisms are present in the biological products.

USDA is authorized to issue three types of permits for importing biological products into the United States (9 CFR 104.2). A separate United States Veterinary Biological Product permit is required for each shipment of biological product to be imported.

Permits are required for imported biological products used for research and evaluation, distribution and sale, or transit shipment only. Requests for application (U.S. Form 14–5) should be submitted to the Veterinary Biologics Staff, Veterinary Services, Animal and Plant Health Inspection Service, 6505 Belcrest Road, Hyattsville, Maryland 20782.

To provide guidance to current or prospective manufacturers employing modern biotechnological methods, the following points are presented:

1. *Recombinant DNA-Derived Products.* Genetic information coding for a product of interest and other sequences not indigenous to the host are referred to as foreign DNA. Recombinant DNA technology encompasses the isolation, characterization, and expression of foreign DNA in organisms or vectors. The specific cloned nucleotide segment coding for the desired product or other foreign DNA segments must be defined in data supporting each license application. These data must also include a description of the source of the DNA and the nucleotide sequence.

A vector is a cloning vehicle which provides a suitable origin of replication necessary for production of foreign DNA. Such replicons may be derived from plasmids, bacteriophages or viruses such as vaccina, bovine papillomavirus, adenoviruses, or SV–40.

Production of functional gene products depends on the efficient expression of cloned DNA-vector complexes in suitable host organisms. Tissue culture cells, bacteria, yeasts, and virus cells may be used as hosts for replication of vectors. The mechanisms of transfer, the copy number, and the physical state of the constructed vector inside the host cell, integrated or extrachromosomal, must be described.

USDA's licensing procedure for veterinary biological products derived from recombinant DNA involves a careful evaluation of each product on an individual basis to assure purity, safety, potency, and efficacy. Scientific and safety considerations may require specific safeguards and procedures in some situations. The USDA strongly recommends that all applicants establish Institutional Biosafety Committees which follow applicable provisions of the NIH Guidelines for Research Involving Recombinant DNA Molecules. USDA intends to propose guidelines which specifically relate to veterinary biological products. Amendments of the regulations and standards dealing with veterinary biologics will also be considered.

2. *Chemically Synthesized Antigens.* When the product consists of chemically synthesized polypetides, the appropriate amino acid sequences will mimic the antigenic site or epitope found in the native antigen where one exists. Procedures used to increase or prolong an immune response, such as coupling to carrier proteins or addition of adjuvants, must also be described. Immunological data derived from chemically synthesized peptides must be as definitive as those from natural antigens.

3. *Monoclonal Antibody Products.* The specificity and potency of monoclonal antibody will be compared with those of similar polyclonal antibody products where appropriate. The sensitivity and specificity of monoclonal antibody products used in diagnostic test kits and their potency characteristics when used therapeutically must be similar to conventional antibody. Monoclonal antibody must be derived from Master Cell Stocks which meet the applicable requirements of 9 CFR 113.52. In addition, as is currently required, a description of cell cloning procedures, preparation, and characterization of cell passages must also be provided.

The Outline of Production must describe all processes including scale-up, ascites fluid or cell culture supernatant preparation, purification, concentration, and inactivation. Mouse colonies must be screened to demonstrate freedom from adventitious agents, especially those detected by the mouse antibody production (MAP) test. If the MAP test discloses the presence of adventitious agents, the product shall not be released unless inactivation procedures approved by Veterinary Services have been performed and tests conducted to ensure proper application of the procedures.

4. *Master Seeds.* Bacterial or viral seed stocks used to prepare veterinary biological products must meet established procedures used to certify Master Seeds for biological products.

The Master Seed for recombinant DNA-derived products may consist of a plasmid or virus carrying the inserted gene. This constructed plasmid is then introduced into the appropriate eukaryotic or prokaryotic expression system selected for vaccine production. Genomic DNA may also be transfected directly into a variety of mammalian cells. Alternatively, in such cases, the stable transfected cell could be considered as the Master Seed.

The establishment of Master Seeds consisting of constructed plasmids or transfected cells requires submission of background information concerning the recombinant DNA procedures used to isolate, purify, and identify genetic material from one source and the modification used for inserting of this material into a new host. Data from cloning, isolation, proliferation, and selection of genetically unique cells would be retained by licensed applicants. In order to characterize adequately the foreign DNA used to code for a particular antigen, the manufacturer must provide a nucleotide sequence analysis.

Tissue culture-propagated cells from vertebrate animals used for vector propagation and antigen production must meet the requirements of 9 CFR 113.51 or 113.52.

If a Master Seed has been accepted by Veterinary Services for use in a licensed product, further genetic modifications may be approved with reduced

requirements for additional host animal efficacy studies.

Each Outline of Production must be prepared in accordance with 9 CFR 114.9. Outlines must include procedures to ensure consistency in production and recovery of specific antigenic material. Recovery procedures must include removal of excessive antibiotic levels (9 CFR 114.10) and undesirable fermentation byproducts such as excessive levels of bacterial endotoxins. Serial release tests for purity, safety, and potency will be required. In addition product characterization tests may be required to demonstrate consistent gene expression.

Organisms and Vectors

Pursuant to the Act of February 2, 1903, (21 U.S.C. 111), and the VSTA, USDA has authority to issue such regulations and take such measures as may be deemed proper to prevent the introduction or dissemination into the United States of the contagion of any contagious, infectious, or communicable disease of animals and/or live poultry from a foreign country into the United States or from one State or territory of the United States or the District of Columbia to another. The importation into the United States or interstate shipment of organisms and vectors is regulated under 9 CFR Part 122. Organisms and vectors are defined in 9 CFR 122.1 as entities which may introduce or disseminate any contagious or infectious disease of animals. Such substances may not be shipped interstate or imported without a permit. Permit applications must completely describe the substances, intended use, location of the permittee, and safeguards.

A number of revised administrative and technical provisions have been instituted to expedite the USDA review and issuance of permits for importation or organisms and vectors which include cell cultures and hybridomas. No animal-origin biological materials, such as cell cultures, monoclonal antibodies, organisms, vectors, or related material, may be imported into the United States without a Veterinary Services (VS) Permit (VS Form 16–3A). To obtain a permit, an application (VS Form 16–3) should be submitted to: Import-Export Staff, Organisms and Vectors, VS, APHIS, USDA, 6505 Belcrest Road, Hyattsville, MD 20782. This is different from the permit required to import veterinary biologics pursuant to Part 104 of the USDA regulations governing such products (VS Form 14–5 and 14–6).

Applicants must also complete the questionnaire entitled "Importation Information" and submit it with their application. Based upon the information submitted by the applicant, a determination will be made if the material to be imported requires safety testing to ensure it is free from livestock pathogens. Safety testing is conducted at the Foreign Animal Disease Diagnostic Laboratory (FADDL), Plum Island, New York.

Applicants will be advised if a safety test is required and will be given an estimate of the cost for conducting the test. Applicants desiring to have material safety tested must enter into a Cooperative Trust Fund Agreement with APHIS, VS, and deposit in advance sufficient funds to cover the estimated cost. The Import-Export Animals and Products Staff will initiate the Cooperative Trust Fund Agreement. In order to expedite the procedure, VS may issue a permit for the material to be shipped to FADDL pending receipt of the funds and Cooperative Trust Fund Agreement. However, the signed Cooperative Agreement, plus the necessary funds, must be received by VS before testing can be scheduled at FADDL.

Usually 60 to 90 days is needed for issuing a permit for importing material to Plum Island, New York, the completion of safety tests, and the transfer of the imported material to the applicant. A minimum of four vials, each containing at least 1 million cells from a uniform lot, is required for the safety testing.

When the test is completed and a determination made that the imported material is free from livestock pathogens, the remainder of the imported material is released directly to the importer under conditions specified in the permit.

If an importer wishes to import cell cultures and/or hybridoma cells on a regular basis, the applicant may enter into a continuous Cooperative Trust Fund Agreement with VS and establish an escrow account to ensure that unnecessary delays will not occur due to insufficent funds.

Each safety test utilizing susceptible host animals usually cost approximately $2,000 to $3,000. Sometimes it is possible to reduce the cost by pooling samples in one host animal test. Scientists at FADDL developed in vitro safety tests to detect certain livestock pathogens resulting in substantial cost savings for importers. The current cost of each in vitro test is approximately $500, depending upon the type of animal disease present in the country of origin as well as the intended use of the imported material.

Safety testing may not be required for some cell cultures imported for human diagnostic purposes and research. Examples of material which could enter without safety testing include cultured human bone marrow cells, amniocentesis samples, and cells imported for karyotype analysis. Applications for such cell cultures will be considered individually.

Permit applications are evaluated by a new classification scheme that correlates intended use of imported cell cultures with the level of safety testing conducted at FADDL.

The following classification of cell cultures is based on intended use and generally indicates the level of safety testing required.

Class I Cell cultures to be used for the production of products such as vaccines, hormones, or other biologicals to be used in livestock, poultry, or for commercial distribution.

Requirement: These cell cultures must be safety tested at FADDL using susceptible host animals, approved in vitro test, and/or laboratory animals.

Class II Cell cultures to be used only for in vitro studies and not to be used in animals other than primates.

Requirement: These cultures may not require safety testing. The material may be sent directly to the importer when no safety testing is required. The permit (VS Form 16–3A) will specify restrictions such as "FOR IN VITRO LABORATORY TESTS: DO NOT INOCULATE INTO LIVESTOCK, BIRDS, OR LABORATORY ANIMALS."

Cell cultures imported under permit which do not require a safety test may not be distributed to other laboratories without prior approval from USDA, APHIS, VS. Applications for the distribution of imported material should be submitted to the USDA, APHIS, VS, Import-Export Staff, Organisms and Vectors.

When appropriate, a review is conducted by the Administrator's Parent Committee on Organisms and Vectors. Members of this committee have wide expertise in evaluating safety. Clearance may also require testing in high security facilities at the Veterinary Services, FADDL, Plum Island, New York.

B. Plants and Plant Products

Pursuant to the authority granted by the Federal Plant Pest Act (FPPA) of May 23, 1957, as amended (7 U.S.C. 150 aa through 150 jj), and the Plant Quarantine Act (PQA) of August 20, 1912, as amended (7 U.S.C. 151 through 164, 166, and 167), USDA has regulatory authority over the movement into or within and through the United States of

plants, plant products, plant pests, and any product or article which may contain a plant pest at the time of movement. These articles are regulated in order to prevent the introduction, spread, or establishment of plant pests new to or not widely prevalent in the United States. The regulations implementing this statutory authority are found in 7 CFR Parts 300 through 399.

"Plant Pest," as defined by statute, means any living stage of any insects, mites, nematodes, slugs, snails, protozoa, or other invertebrate animals, bacteria, fungi, or parasitic plants or reproductive parts thereof, viruses, or any organisms similar to or allied with any of the foregoing, or any infectious substances, which can directly or indirectly injure or cause disease or damage in any plants or parts thereof, or any processed, manufactured, or other products of plants (7 U.S.C. 150aa(c)).

"Movement," as defined by statute, means to ship, deposit for transmission in the mail, otherwise offer for shipment, offer for entry, import, receive for transportation, carry, or otherwise transport or move, or allow to be moved, by mail or otherwise (7 U.S.C. 150aa(g)).

The current permit system requirements for the movement into or within and through the United States of plants, plant products, plant pests, and other articles regulated by FPPA and PQA were fully described in the December 31, 1984 Notice at 49 FR 50900–01. The procedures for issuing permits for the movement of plant pests were discussed separately from plants, plant products and other articles which may contain plant pests at 49 FR 50901–02. USDA regulates the importation of noxious weeds through a permit system similar to that established for plant pests. The existing regulations in 7 CFR Part 360 which designate plants as noxious weeds and establish procedures for obtaining an import permit were described at 49 FR 50902.

Regulation of the Introduction of Organisms and Products Altered or Produced Through Genetic Engineering Which Are or Which There Is Reason to Believe Are Plant Pests

The FPPA and PQA are applicable to the movement of plants, plant products, and other articles and plant pests developed through genetic engineering if such plants, plant products, other articles, or plant pests present a risk of plant pest introduction, spread, or establishment.

Under the authority granted by the FPPA and PQA, USDA is proposing new regulations which would impose restrictions on the introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests.

In accordance with the provisions of the FPPA and PQA, USDA must determine the plant pest status of plants, plant products or articles to be moved into or within or through the United States. The evaluation process for determining what safeguards, if any, can be imposed which would allow the movement of the plant pest without risk that the plant pest would be disseminated were described in the December 31, 1984 Notice at 49 FR 50901–02. For genetically engineered material from dissimilar source organisms (inter-generic combinations), the determination may be complex. Information about genetically engineered organisms produced through the use of donor, vector/vector agent and recipient organisms that are from a list of known plant pests is needed in order that such organisms be properly regulated.

During the past year, USDA has received permit applications to move genetically engineered organisms into or through the United States. USDA is confident that organisms altered through genetic engineering will play a major role in increased plant yield and improved plant quality. However, a genetically engineered organism derived from organisms that are plant pests also presents a risk of plant pest introduction. The organisms themselves, the cultures in which they are transported, or their packaging may be contaminated with plant pathogens. Genetic alteration may create a plant pest new to and not widespread in the United States. It is necessary, therefore, to establish appropriate safeguards to prevent the introduction of genetically engineered organisms that pose a threat to agriculture. Other genetically engineered organisms that are not plant pests or where there is no reason to believe such organisms are plant pests would not be regulated.

New data have to be required in order to properly evaluate permit applications for those organisms which are plant pests or which there is reason to believe are plant pests. A determination was made that additional data requirements would be incorporated into proposed regulations for those genetically engineered organisms which are of concern under the provisions of the FPPA and PQA.

USDA is publishing as a companion document in the "proposed rules section" of this issue of the **Federal Register** its proposed regulations pertaining to organisms and products altered or produced through genetic engineering which are on plant pests or which there is reason to believe are plant pests.

The proposed regulations would establish a new part entitled, "Introduction of Organisms and Products Altered or Produced Through Genetic Engineering Which Are Plant Pests or Which There is Reason to Believe are Plant Pests", in Title 7 of the Code of Regulations (7 CFR), pursuant to the authority of the FFPA, as amended (7 U.S.C. 150aa–150jj) and the PQA, as amended, (7 U.S.C. 151–164, 166, 167). Such proposed regulations would regulate the importation into and movement within and through the United States as well as prevent the release into the environment of certain organisms, or products altered or produced through genetic engineering, which are plant pests or which there is reason to believe are plant pests.

The proposed regulations would restrict the "introduction" of certain organisms and products altered or produced through genetic engineering, referred to as "regulated articles." In this context, "introduction" means to move into the United States, to release into the environment, or to move interstate, or any attempt thereat." "Release into the environment" means "use of a regulated article outside the constraints of physical confinement that are found in a laboratory, contained greenhouse, or fermenter or other contained structure."

USDA's proposed regulations, which are designed to prevent the release into the environment of genetically engineered organisms which are plant pests or which there is reason to believe are plant pests are consistent with the legislative intent of the FPPA. The FPPA was enacted in 1957 and was intended as "gap filling" legislation for the purpose of protecting American agriculture against invasion by plant pests and diseases which are new to or not theretofore known to be widely prevalent or distributed within and throughout the United States. The FPPA also provides USDA with authority to regulate insects or pests that might later be found to be injurious to cultivated crops. The release into the environment of a genetically engineered plant pest is tantamount to the introduction of a plant pest which is new to and not theretofore known to be widely prevalent within and throughout the United States and subject to regulation under the FPPA.

It should be noted that "regulated article" would be defined as any organism or product altered or produced through genetic engineering, if the donor

organism, recipient organism, or vector or vector agent belongs to a group of organisms designated by the proposed regulations as having plant pests or any organism or product which USDA determines is a plant pest or which there is reason to believe is a plant pest. Under USDA's proposed definition, certain microorganisms would be excluded if the recipient microorganism is non-pathogenic, is non-infectious, and otherwise not a plant pest, and resulted from the addition of genetic material that is well characterized and contains only non-coding regulatory regions. Restrictions would be required for regulated articles because they are plant pests, or because USDA has reason to believe they are plant pests. The proposed regulations would require that a person obtain a permit prior to the introduction of a regulated article and would list specific conditions required for the introduction of a regulated article. The regulated article could be introduced only if all conditions in the proposed regulations as well as all conditions specified on the permit were met. It is important to note that in considering whether a permit can be issued for the introduction of a genetically engineered organism, USDA will perform the same comprehensive analysis that is used in determining whether a permit can be issued for the movement of a "conventional" plant pest. Such asessment shall include an examination of the factors that were discussed in the December 31, 1984, Notice at 49 FR 50901–02 as part of the evaluation process for determining what safeguards can be imposed which would allow the movement of a plant pest without risk of dissemination. These factors are oriented toward an examination of the ecological and environmental effects of a release of the genetically engineered organism or product into the environment.

The proposed regulations also contain provisions for a certificate of exemption for those organisms or products altered or produced through genetic engineering that are not subject to the proposed regulations. A person seeking to introduce an exempt article could voluntarily request a certificate of exemption to facilitate the introduction of the organism or product.

The proposed regulations provide a list of groups of organisms which are plant pests or contain plant pests. If the donor, vector/vector agent, or recipient of the genetically engineered organism is derived from an organism on the list of organisms containing plant pests, such genetically engineered organism would be deemed a "regulated article".

As defined in the proposed regulations, a plant pest includes microorganisms such as bacteria and viruses, and thus a "regulated article" may be a microorganism unless it meets the provisions for exclusion. It is important to note that in some instances certain microorganisms will be subject to joint regulation by USDA and EPA. USDA has jurisdication over certain microorganisms under the FPPA and PQA if the microorganisms are a plant pest. EPA would have jurisdiction under the Toxic Substances Control Act (TSCA) if the microorganism is deemed to be a "new" microorganism or under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended (FIFRA) if the microorginism is to be used as a pesticide. Because each Agency has a different statutory mandate, certain jurisdictional overlaps cannot be avoided. However, EPA and USDA will work cooperatively and simultaneously in the evaluation of genetically engineered microorganisms that fall under the jurisdication of both Agencies. To expedite the review of these microorganisms each Agency will appoint contact persons to coordinate the review to ensure data requests are not duplicated.

The specifics of which microorganisms will be subject to dual Agency review, or primarily single Agency review, is set forth in the preamble of USDA's proposed regulations being published as a companion document to this policy statement. That document should be consulted for further information.

A key to determining whether a genetically engineered organism will be regulated by USDA is the list of organisms containing plant pests that appears in § 340.2 in proposed Part 340. USDA acknowledges that this is not an exhaustive list, and that it does not attempt to list every pest species. Comments are welcome on the list as well as on other parts of the proposed regulations.

In order to solicit as many comments as possible on the list and all other parts of the proposed regulations, USDA has scheduled public hearings in Washington, DC and Sacramento, California, during the 60-day comment period. The time and place of the public hearings as well as the address to send written comments is specified in the preamble to the proposed regulations.

USDA believes that through the submission of detailed comments and full participation by public and private interests, USDA will be able to promulgate a final regulation that will prevent the introduction and dissemination of genetically engineered organisms which are plant pests or which there is reason to believe are plant pests, yet not impede the development of biotechnology.

C. Meat and Poultry Products

The Food and Safety Inspection Service (FSIS) is responsible for assuring the safety, wholesomeness, and proper labeling of food products prepared from domestic livestock and poultry. The Federal Meat Inspection Act (FMIA) and the Poultry Products Inspection Act (PPIA) require FSIS to inspect cattle, sheep, swine, goats, equines, poultry, and food products prepared from them which are intended for use as human food to assure that they are wholesome, not adulterated, and properly labeled, marked, and packaged. Inspection under these statutes is mandatory. The cost of inspection, except for overtime and holiday inspection work, is required to be borne by the USDA. Food, animals and animal products, other than those required to be inspected under the FMIA and PPIA, may be inspected under a voluntary, reimbursable inspection program established under the Agricultural Marketing Act of 1946.

Within the framework of food safety statutes, FSIS has developed regulations for research on animals that are administered experimental animal drugs, biologics, and pesticides (9 CFR 309.17 and 381.75). These regulations state that no animal used in any research investigation involving an experimental biological product, drug, or chemical shall be eligible for slaughter at an official establishment unless certain conditions are met. These conditions include any of several different ways of demonstrating that the use of such biological product, drug, or chemical will not result in the products of such animals being adulterated.

Products Subject to Review. FSIS anticipates that many food animals which are subject to the new techniques of modern biotechnology will not differ substantially in appearance, behavior, or general health from currently inspected cattle, sheep, swine, goats, equines, and poultry. They would be subject to the same inspection procedures and regulations as tradionally inspected food animals. FSIS is aware that some genetically engineered animals, such as mosaics, chimeras, and some hybrids, may differ substantially from animals that are inspected currently under the FMIA and PPIA. If such animals are ever intended for use as human food and are presented for inspection at an official

establishment, a decision would have to be made as to whether such animals were covered under the FMIA or PPIA, and if not, whether the FMIA and PPIA should be amended to require inspection of such animals and their products.

Implementation of Review Authority. FSIS's approach toward the review of food animals resulting from the techniques of moderm biotechnology consists, in general, of two phases. The first, an experimental phase, focuses on the experimental aspects of vector administration, gene transfer and gene expression. Since artificial vectors used in animal gene transfer may be considered as either animals drugs or animal biologics, their administration to food animals would be covered under the current regulations on animals used for research (9 CFR 309.17 and 381.75). The requirement that an animal carcass intended for use as human food not be adulterated may require that certain phenotypic, biochemical, and microbiological parameters not be exceeded before the animal can be slaughered for human food. Depending on future developments, FSIS may amend the regulations (9 CFR 309.17 and 381.75) to provide further assurance that the products of animals genetically engineered by certain techniques are not adulterated. The second phase would be carried out under existing regulations (9 CFR Parts 301 through 381) and would focus on the commercial development, production, inspection and labeling of food animals and food animal products.

D. Seeds

The Federal Seed Act (FSA) (7 U.S.C. 1551 *et seq.*) defines USDA regulatory authority over the importation and interstate shipment of agricultural and vegetable seeds. It does not apply to the production or intrastate distribution of seeds or to seeds other than agricultural or vegetable seeds ("agricultrual seeds" are grass, forage, and field crop seeds).

The FSA prohibits interstate shipment of seed that contains noxious weed seeds at levels in violation of the laws of the State of destination or in excess of levels allowed by the Secretary of Agriculture. This provision applies primarily to seed adulterated with noxious weed seed. In a few instances, however, States have determined that a particular variety of agricultural or vegetable seed is itself a noxious weed. In these instances, FSA prohibits the interstate shipment of the seed into those States. The FSA also allows the Secretary to prohibit the importation of agricultural and vegetable seed which is adulterated with noxious weed seed or which is unfit for seeding purposes.

The authority granted to the Secretary by the FSA to prohibit the interstate shipment or importation of seeds which are found to be detrimental to the agricutural interests of the United States applies to seeds genetically engineered with the modern biotechnology to the same extent as any other seeds.

V. Scientific Review Mechanisms

The manner in which both regulation and oversight of research in agriculture-related biotechnology evolves and is implemented in the United States will have a direct impact on the competitiveness of U.S. industry in both domestic and world markets. Inconsistent or unnecessary procedures for regulation and research will place the U.S. scientific effort and U.S. producers at a substantial disadvantage. It also is important that safeguards be built into biotechnological research processes, and that releases be based on careful evaluations while further experience is being gained. Therefore, USDA feels that such regulatory and research decisions must be based on the best science available.

While the responsibilities within USDA for biotechnology reside with the Assistant Secretary for Science and Education and the Assistant Secretary for Marketing and Inspection Services as the delegates of the Secretary of Agriculture, in carrying out their respective responsibilities based on the best science available, they would be able to take advantage of the expertise and perspectives within the Federal Government through a committee to be called the Committee on Biotechnology in Agriculture (CBA). The CBA, to be chaired by these two Assistant Secretaries, will function both as a policy body in the USDA and a bridge between its research and regulating structures.

Committee on Biotechnology in Agriculture

The objectives of the CBA will include:

—To provide advice, when requested, on initiatives, proposals, and policy for agriculture-related regulation and research, and assist in the coordination of these activities;
—To review scientific issues submitted by agencies within the Department;
—To assist in identifying data gaps for basic research in agricultural biotechnology;
—To foster public awareness of the scientific issues in biotechnology;
—To provide Departmental support for participation in the FCCSET BSCC.

USDA expects that the CBA also will utilize existing cooperative entities (e.g., other Federal agencies, universities, State regulatory officials, the public sector, and industry) to acquire, when necessary, information for addressing those issues submitted to it. Such entities, when requested, can provide technical support for sound regulatory and research decisions regarding the use of biotechnology in agriculture and foresty. These entities offer a vast scientific resource upon which USDA can draw.

VI. Summary of Comments

USDA received the comments of one hundred-two (102) respondents, one-half of whom commented specifically on the USDA policy statement. Although USDA agencies considered all comments on the coordinated policy proposal, this response is confined to comments on the USDA portion of the notice.

The two largest categories of respondents were business and academic, followed closely by associations representing these interests. Comments came in lesser numbers from environmental and public interest groups, individuals, law firms, and foreign governments, as well as the National Institutes of Health Recombinant DNA Advisory Committee (NIH–RAC) and a member of the U.S. Congress

The USDA response to the comments follows the form of the original notice, with a discussion of comments on regulatory philosophy followed by a response to comments on the regulatory framework.

Comments on the Nature of Products of Modern Biotechnology: Fourteen respondents stressed their agreement with the USDA statement that "agriculture and forestry products developed by modern biotechnology will not differ fundamentally from conventional products," while six commenters dissented. Three respondents felt that genetic engineering across species barriers did create a potentially different product and the possiblity of unique ecological effects. Concern about the "need for public trust" and public assurance on safety and ethical issues was stressed by three commenters. Seven respondents agreed with USDA that "to date, no unique or safety problems have been associated with products of genetic engineering," but four of the same commenters who view biotechnology products as fundamentally different from conventional products stressed that the potential exists for safety problems with biotechnology applications.

Response: USDA recognizes the importance of ecological effects and the need for developing procedures responsive to public concerns about safety.

Although USDA's regulatory philosophy remains as stated, additions to regulatory procedures are being proposed for genetically engineered plants and plant products and veterinary biologics produced by biotechnology (see section IV). The previously discussed delegations of authority within USDA for biotechnology increase the effectiveness of the administration of current and proposed regulatory procedures affecting the products of modern biotechnology.

For veterinary biological products, USDA is currently developing additional procedures pursuant to the VSTA, as amended, for evaluating requests to conduct experimental field trials with live vectors containing genetically engineered organisms or to support product license applications. The procedures being developed consider the parental organism and the effect of the gene alteration on the genetic properties of the recipient, especially the survival, reproduction, and dispersal characteristics. A careful analysis of the genetics, biology, and ecology of the wild-type and modified microorganisms will provide as reasonable prediction of the risks which might be associated with use of the altered organisms.

USDA is proposing regulations pursuant to the Federal Plant Pest Act (FPPA) and the Plant Quarantine Act (PQA) for regulating the introduction of certain organisms of products thereof altered or produced through biotechnology which are plant pests or may become plant pests. This proposed rule should assist USDA in assessing the ecological effects of the release of such genetically engineered organisms into the environment.

Guidelines for oversight of agricultural biotechnology research funded by USDA will be issued under the authority of the Food Security Act of 1985.

USDA also is establishing scientific review mechanisms to assist in research and regulatory decisions (see section V).

These proposed modifications in the procedural framework are described as a part of the final policy statement for veterinary biologics, plants and plant products, research, and scientific review mechanisms.

Comments of the Adequacy of Existing Authority: Thirteen commenters agreed with USDA that its existing regulatory framework is adequate for biotechnology applications, and nine favor the case-by-case approach under existing authority. Five commenters felt that new legislation is or may be needed; two of the five oppose the case-by-case approach.

Response: USDA has examined its statutory authority for regulating biotechnology products and processes, and USDA agencies have processed licensing and permit applications under the existing statutes. The existing authority is considered adequate at this time. Established procedures, with the proposed modifications, can be adapted effectively to handle biotechnology applications. USDA is currently considering genetic engineering applications on a case-by-case basis using existing authority.

Comments on Need for Procedures and Guidelines: Sixteen respondents commented that USDA had not outlined procedures for the review and approval of genetically engineered products. Twelve respondents stressed the need for flexibility, and six requested sunset provisions in USDA biotechnology regulations.

Response: The USDA policy statement of December 31, 1984, did outline procedures currently used for the review and approval of certain genetically engineered products. In considering license applications for genetically engineered veterinary biologics, USDA follows the standards and procedures applicable to all such products found in §§ 101–117 of the applicable regulations and standards (9 CFR 101–117). In the December 31, 1984 Notice, USDA offered supplementary guidelines for licensing such products. New procedures are being developed to evaluate production and testing of veterinary biologics derived through use of genetic engineering techniques. The information needed for proper evaluation will depend on the parent organism and the effect of the gene alteration on the genetic properties of the recipient. A paper describing the USDA licensing policy for biologics produced by recombinant DNA technology was presented at the Joint International Association of Biological Standardization/World Health Organization Symposium on "Standardization and Control of Biologics Produced by Recombinant DNA Technology," Geneva, Switzerland, 1983 (published in *Developments in Biological Standardization*, V. 59, pp. 167–173, S. Korgel, Basel, 1985). The paper describes requirements for plasmid/vector characterization and stability, and correlation to conventional Master Seed concepts, as well as methodology which can be used to monitor antigenic expression, concentration, purification, and stability testing during production and recovery.

The movement of genetically engineered products which are plant pests and present a risk of plant pest introduction or spread is regulated by 7 CFR 330.200 implemented pursuant to the FPPA and PQA. The movement of organisms and vectors which may cause desease in animals is regulated under 9 CFR Part 122.

USDA realized that the statement left unanswered some questions about the means for review and approval of various genetically engineered products. The proposed regulations described in section IV(B), implemented under the authority of the FPPA establish permit requirements for the "introduction" of organisms altered or produced by genetic engineering which are or may become plant pests. The regulations would be flexible because organisms determined not to be plant pests would be exempt, and this category could be expanded in the future to include organisms whose plant pest status is currently uncertain and therefore restricted. It is hoped that the discussion in section IV(B) of this policy statement answers any remaining questions about the review and approval procedures for such genetically engineered products.

Comments on Confidential Business Information (CBI): Six commenters representing business and scientific interests expressed concern about the protection of "confidential business information" in the USDA regulatory process while two public interest groups stressed the "public's right to know."

Response: The USDA regulations implementing the Freedom of Information Act (FOIA) (5 U.S.C. 552) are found in 7 CFR 1.1–1.16. The FOIA provides that Federal agencies must make available to the public all records not specifically exempt from disclosure. Exemptions include "trade secrets and commercial or financial information," (5 U.S.C. 552(b)(4)). On September 23, 1985, USDA's APHIS issued a policy statement on the protection of privileged or confidential information (50 FR 38561–38563). This policy statement establishes requirements for the control and protection of documents received by APHIS that contain privileged or confidential business information concerning biotechnology and the veterinary biologics program. The procedures established conform to the FOIA requirements for both protection and disclosure.

Comments on Use of NIH Guidelines: Four respondents questioned the USDA requirements that manufacturers of

veterinary biological products using recombinant DNA technology follow the National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines). One respondent thought USDA implied that all people "who work with recombinant DNA plants" would be required to comply with the NIH Guidelines, and requested procedural guidelines for industry.

Response: The USDA does not require that the manufacturers of veterinary biological products or plant products of recombinant DNA technology follow the NIH Guidelines. However, USDA strongly recommends that all license applicants for veterinary biologics follow appropriate provisions of the NIH Guidelines, such as those regarding the establishment of an institutional biosafety committee. USDA intends to propose guidelines that will parallel closely the NIH Guidelines, and it intends to recommend strongly that entities not required to follow the USDA guidelines do so voluntarily.

Comments on Importation of Cell-Lines: Three associations representing biotechnology companies requested that USDA take steps to reduce delays in the clearance and testing procedures required for the importation of biotechnology-derived products and cell-lines. On February 12, 1985, the Association of Biotechnology Companies (ABC) delivered a report on USDA importation guarantine issues to the APHIS Parent Committee for Foreign Pathogens and Vectors. This report was an attachment to the ABC comment letter.

Response: The USDA has instituted a number of revised administrative and technical provisions to expedite the issuance of permits for importation of organisms and vectors which include cell cultures and hybridomas. A supplementary questionnaire, designed to insure adequate information on cell cultures and products from recombinant DNA or hybridoma technologies, now accompanies each permit application. Applicants are advised whether or not a safety test is required and a cost estimate is given. Safety testing may be conducted concurrently with the administrative review of the permit application, but only at APHIS' Foreign Animal Disease Diagnostic Laboratory (FADDL) at Plum Island, New York. New test procedures have reduced the cost of safety testing, and the cost per sample can be further reduced by conducting a safety test with pooled samples. Permit applications are evaluated using a new classification scheme that equates intended use of imported cell cultures with the level of safety testing required at FADDL. Class I cell cultures, employed in the preparation of products such as enzymes, vaccines, or hormones for commercial use, are subject to complete safety testing. Class II cell cultures, used only for in vitro studies and not to be used in animals other than primates, are subject to a lesser degree of testing.

Comments on Risk Analysis: Seven respondents discussed the issue of risk assessment or risk/benefit analysis of biotechnology applications. Comments varied from a recommendation that "standard risk assessment methodologies" be adopted by all agencies to a warning against attempting to regulate the "hypothetical and imaginary "potential' dangers" of recombinant DNA techniques.

Response: The National Environmental Policy Act (NEPA) applies to USDA actions. The "APHIS Guidelines Concerning Implementation of NEPA Procedures" (44 FR 50381, August 28, 1979) would be used to make an environmental assessment or environmental impact statement of the effects of a proposed release of a genetically engineered organism regulated pursuant to the VSTA, the FPPA and PQA, and related statutes. A formal risk management procedure based on a wide variety of safety concepts will be used to evaluate systematically proposed releases. The information required by any new regulations promulgated under the FPPA and PQA would be used to prepare the environmental assessment for release of a genetically engineered product which is a plant pest or may become a plant pest.

In normal husbandry and laboratory practices, veterinary biological products normally are not considered to be released into the environment. In the event that a conventionally prepared or recombinant derived product would be considered to be released into the environment, the issuance of a license or import permit would require compliance with procedures being developed and interagency approval. The procedures under development consider the parental organism and the effect on the gene alteration on the genetic properties of the recipient, especially the survival, reproduction and dispersal characteristics.

Safety, ethics, and policy issues in agricultural biotechnology research will be overseen by the Committee on Biotechnology in Agriculture (CBA) and such supporting technical advisory groups as may be established by the USDA agencies. Currently, all USDA and USDA-sponsored research involving recombinant DNA must be cleared prior to initiation for compliance with the NIH Guidelines.

Comments on Jurisdiction: The potential for overlapping jurisdiction in the policy notice drew the largest number of comments. Eighteen respondents pointed out that both USDA and EPA propose to regulate agricultural microorganisms. Respondents representing the interests of the veterinary biologics industry contended that a jurisdictional dispute between USDA and FDA delayed the approval of bovine interferon. While generally supporting the concept of the memorandum of understanding (MOU) between USDA and FDA to resolve jurisdictional disputes, one respondent challenged the legality of the MOU, noting that it contains the statement that "animal biological products generally act through a specific immune process," while USDA's current regulations do not restrict its jurisdiction to products operating through such a mechanism of action. Industry respondents also pointed out that the intrastate producer of veterinary biologics is not regulated by USDA. Two firms and one industry association urged prompt Federal oversight action so that States do not act independently to regulate biotechnology products.

Response: USDA agrees that there is the potential for overlapping jurisdiction among the Federal agencies involved in regulating biotechnology products. USDA and EPA representatives have discussed jurisdiction over genetic engineering applications since 1983. USDA and EPA have begun to establish a regulatory procedure for reviewing certain submissions of genetically engineered microorganism applications, a procedure which has resulted in joint consultation on several proposals for release into the environment of organisms altered by genetic engineering.

For veterinary biologics regulated under the VSTA, use of procedures currently under development will increase USDA effectiveness in evaluating biotechnology license and product applications. The MOU between USDA and FDA was published on June 8, 1982, in an attempt to resolve the issue of new products which fall into the questionable definitional area between animal drugs regulated by FDA and animal biologics regulated by USDA. An interpretation by some that the term animal biologics only includes substances that act through a specific immune process has resulted in some confusion. There is nothing in USDA's

current regulations or law which restricts its jurisdiction to products acting solely through this mechanism of action, and because of this fact, the memorandum qualifies its reference to specific immune process by the word "generally." Although efforts will be made to clarify the issue further, it should be noted that there appears to be little uncertainty about whether a particular product is a veterinary drug or biologic.

The Food Security Act of 1985 contains amendments to the VSTA that extend USDA's jurisdiction to veterinary biologics which are shipped intrastate or exported. The provisions of the amendments are discussed more fully in Section IV.

Comments on the National Biological Impact Assessment Program (NBIAP): Seven respondents commented on the NBIAP, the proposal by the National Association of State Universities and Land Grant Colleges (NASULGC) for establishing a program to assess genetically engineered organisms before they are released into the environment. Three commenters—a member of Congress, a spokesperson for a biotechnology firm, and an officer of an environmental organization—posed questions about the proposal. The questions concerned the NBIAP's statutory or regulatory status; its relation to other USDA agency operations and other Federal agency operations; the processes of risk assessment to be used; its adequacy to review an increasing volume of products; and the appropriateness of biohazard committees as vehicles for review of commercial processes and products. Four respondents representing NASULGC institutions endorsed the proposal stating the view that the agricultural research community has the capability to develop guidelines and assess impacts of biotechnology research and commercial products. The major goal of the program was thought to be insuring the safety of society and the environment.

Response: NBIAP is a scientific advisory system that would be available to the Assistant Secretary for Science and Education. By this system the USDA can draw upon the best experience available from scientists in universities, Federal laboratories, and industry to help assess the risks involved in the processes and products from RDNA work in biotechnology.

NBIAP shall act in an advisory capacity and is in no direct way a part of the formal approval process. It is available to provide assessment, but is not a mandatory process.

Comments on Definitions, Terms, and Data Requirements: Five respondents recommended changes in the definitions, terms, data requirements or classification used by USDA in the notice. Each recommendation is discussed below.

Two respondents commented on the USDA statement of licensing policy for veterinary biologics produced by modern biotechnical methods at 49 FR 50899–50900. Under the heading "1. Recombinant DNA-Derived Products," a manufacturer of veterinary biologics questioned the need to provide the entire nucleotide sequence of a foreign DNA being cloned into a vector.

It is USDA's position that in order to characterize adequately the foreign DNA used to code a particular antigen, the manufacturer should provide a nucleotide sequence analysis. The construction of the vector used for expression of the cloned nucleotide sequence also should include source and function of the component parts of the vector, i.e., origin of replication, antibiotic resistance genes, promotor, enhancers, etc. The manufacturer also questioned the data requirement under the heading "2. Chemically Synthesized Antigens" concerning the persistence of the immune response following administration of the synthetic peptide. The USDA feels that a major concern with the use of synthetic peptides is the development persistence of the immune response. USDA does not intend to require more stringent efficacy data than that necessary to support a veterinary biologic license application employing natural antigens. However, immunological data derived from chemically synthesized peptides must be as definitive as the serological response from natural or nonsynthetic antigens. With respect to the next sentence in the policy statement, an individual respondent proposed a change from the term "antibody response" to "immune response." It is true that the term used in the sentence "Procedures used to increase or prolong an antibody response . . ." is somewhat limiting and can create confusion between B-cell and T-cell response. Therefore, the recommendation to replace "antibody response" with the term "immune response" is accepted, since both T-cell responses as well as T-cell/B-cell interactions would be included in the statement.

On the subject of plants and plant pests, a plant pathologist commented on the references to *Pseudomonas syringae* as plant pathogens under the heading "ice nucleation negative bacteria" at 49 FR 50902. The respondent noted that none of the strains of *Pseudomonas syringae* currently proposed for use are plant pathogens and that it would be more correct to call *P. syringae* plant-associated bacteria, some of which are pathogens. USDA will clarify future references to these organisms as the respondent suggests. According to current practice, and under the proposed FPPA regulations, an applicant for a USDA permit to import or move *Pseudomonas syringae* would be required to submit data to show whether or not the strain was a plant pest.

Addendum—Research Legislative Authorities

The USDA is authorized under its Organic Act (7 U.S.C. 2201 et seq.) and other legislation to conduct and support research in wide ranging areas of agriculture. Examples of such other laws include:

The Alcohol Fuels Research (7 U.S.C. 3154); the National Latex Commercialization and and Economic Development Act (7 U.S.C. 178–178n); the Animal Health and Disease Research Act (7 U.S.C. 3195); Special Research Grants (7 U.S.C. 450i(c)); The National Aquaculture Act (16 U.S.C. 2801 et seq.); the Cotton Research and Promotion Act (7 U.S.C. 2101 et seq.); the Potato Research Information Act (7 U.S.C. 2611–2627); the Egg Research and Consumer Information Act (7 U.S.C. 701 et seq.); the Beef Research and Information Act (7 U.S.C. 2901 et seq.); the Wheat and Wheat Foods Research and Nutrition Education Act (7 U.S.C. 3401 et seq.); the Animal Cancer Research Act (7 U.S.C. 3901 et seq.); the Floral Research and Consumer Information Act (7 U.S.C. 4301 et seq.); and the Forest Research Assistance Act (16 U.S.C. 582a–582a–7).

DEPARTMENT OF LABOR

Occupational Safety and Health Administration

Agency Guidelines on Biotechnology

AGENCY: Occupational Safety and Health Administration (OSHA), Labor.

ACTION: Announcement of guidelines on occupational safety and health in the field of biotechnology.

SUMMARY: OSHA has reviewed its responsibilities under the Occupational Safety and Health Act of 1970 (29 U.S.C. 651 et seq.) as they relate to the protection of the safety and health of workers in the rapidly developing field of biotechnology. Section 8 of the Act authorizes OSHA to inspect workplaces including laboratories and places of employment relating to biotechnology.

Section 5(a)(1) of the Act requires that each employer furnish to each of his employees employment and a place of employment which are free from recognized hazards that are causing or are likely to cause death or serious physical harm.

OSHA has determined that this general duty clause, together with several specific standards, currently provides an adequate and enforceable basis for protection of the safety and health of employees in the field of biotechnology. No additional regulation of workplaces using biotechnology appears to be needed at this time, or since no hazards from biotechnology per se have been identified. However, if any of the new biotechnology processes cause hazardous working conditions that result in a significant risk of death or serious harm to workers, OSHA will consider regulating unless the worker exposure is effectively controlled under current OSHA standards or another agency has exercised its authority over health and safety matters for those working conditions. Guidelines contained in this notice are provided to: (1) Clarify the relationship of the existing statute to the field of biotechnology, and (2) reiterate commonly employed laboratory safety practices.

FOR FURTHER INFORMATION CONTACT: James F. Foster, Director, Office of Information and Consumer Affairs, Occupational Safety and Health Administration, Room N-3637, U.S. Department of Labor, 200 Constitution Avenue, NW., Washington, DC 20210. Telephone (202) 523-8151.

A. Background

The Occupational Safety and Health Administration (OSHA) published an announcement of guidelines on occupational safety and health in the **Federal Register**, Volume 50, Number 71, page 14483, April 12, 1985 with a request for public comment. All comments received supported the statement although the National Institute for Occupational Safety and Health (NIOSH) recommended increased surveillance because their research indicated gaps in current knowledge.

Biotechnology is the application of biological systems and organisms to technical and industrial processes. The technologies employed in this area include, but are not limited to:

(1) Classical genetic selection and/or breeding for purposes such as developing bakers yeast, conventional fermentation and vaccine development;

(2) The direct in vitro modification of genetic material, e.g., recombinant DA or gene splicing; and,

(3) Other novel techniques for modifying genetic material of living organisms, e.g., cell fusion and hybridoma technology.

Modern biotechnology is analogous to other conventional industrial processes and has great potential benefit to society and wide application to numerous industries. It is considered by some to have economic potential comparable to the microprocessor industry. Genetic engineering has a wide spectrum of applications of commercial importance, but many such applications are in the early stages of development or have been expressed only as concepts.

The Occupational Safety and Health Act of 1970 (OSH Act) grants the Secretary of Labor broad power to require employers to provide a safe and healthful workplace for their employees. Where other Federal agencies exercise their statutory authority to prescribe or enforce standards or regulations affecting occupational safety or health, OSHA is preempted by section 4(b)(1) of the Act.

Section 5(a)(1) of the Act requires employers to furnish their employees with a workplace "free from recognized hazards that are causing or are likely to cause death or serious physical harm." Section 5(a)(2) requires employers to comply with safety and health standards set by the Secretary. The Secretary in establishing standards to deal with toxic materials and harmful physical agents is required by the OSH Act to "set the standard which most adequately assures, to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life" (section 8(b)(5)). Under a recent Supreme Court decision permanent standards can be promulgated only upon a finding by the Secretary that the standard is reasonably necessary to remedy a significant risk of material health impairment. Finally, emergency temporary standards may be promulgated only upon a finding that employees are "exposed to grave danger." (section 8(c)(1).)

In view of the statutory criteria briefly outlined above and the currently known hazards from biotechnology processes there does not appear to be a need for new OSHA regulations. Furthermore, the biotechnology processes, whether present in laboratories, pilot projects or industrial plants, usually involve conventional chemicals and processes that are already covered by OSHA regulations. These conventional processes use solvents or products, some of which may be toxic or dangerous to employee health in certain dosages over certain periods of time. The potentially hazardous character of some aspects of biotechnology is primarily from the chemicals used and not the biotechnology products. Therefore, the regulations that effectively regulate chemical exposures will usually ensure that biohazards too will be controlled. However, when a process employing biotechnology alone or in combination with conventional chemicals and technology presents a significant hazard to employees which cannot be dealt with by existing standards or the general duty clause, OSHA will consider regulating in order to protect employees health. Increased industrial hygiene monitoring and medical surveillance will help to assure worker protection. At this time, no new regulations that would specifically cover biohazards are warranted.

OSHA endorses the BSCC definitions of "intergeneric (new) organism" and "pathogen" found in the preamble, believing they describe the microorganism appropriate for review when environmental or agricultural applications of microorganisms are contemplated. For contained commercial manufacturing processes, these definitions may also properly exclude from review certain microorganisms of known low risk.

OSHA is committed to the policy described in the section entitled "International Aspects" in the Office of Science and Technology Policy General Preamble, published in today's **Federal Register.**

B. Guidelines

As stated above, section 5(a) of the OSH Act requires that each employer:

(1) Shall furnish to each of his employees employment and a place of employment which are free from recognized hazards that are causing or are likely to cause death or serious physical harm to his employees;

(2) Shall comply with occupational safety and health standards under this Act.

Specific standards which may be applicable include:

- Specific air contaminants (29 CFR Part 1910, Subpart Z).
- Access to employee exposure and medical records (29 CFR 1910.20).
- Hazard communication (29 CFR 1910.1200).

• Exposure to toxic chemicals in laboratories (currently in draft and under development).

• Respiratory protection (29 CFR 1910.134) (currently being updated).

• Safety standards of a general nature, for example, general environmental, walking and working surfaces, fire protection, compressed gases, electrical safety, and material handling and storage contained in 29 CFR Part 1910 Subparts J, D, E and L, H, S and N).

Effective biological safety and health programs have been operative in a variety of laboratories for many years. Motivation and critical judgment are necessary in addition to specific safety and health knowledge to ensure protection of personnel, the public and the environment. All personnel directly involved in biotechnological projects should receive adequate instruction so that the potential biohazards can be understood and appreciated. Emergency plans should be formulated for each project where the chemicals used or biotechnical product produced pose a potential safety or health hazard. The plans should describe the procedures to be followed if an accident contaminates personnel or workplaces. If a research group is working with a known pathogen for which an effective vaccine is available, employees should be immunized, as appropriate.

Before biotechnological work is undertaken, it is imporant that management determine the potential hazards involved and the precautions to be taken. Program and support staff should then be advised of the real and potential hazards. Staff should be instructed and trained in the protection and techniques required to ensure safety and in the procedures for dealing with accidentally created hazards.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of Policy

AGENCY: National Institutes of Health, PHS, DHHS.

ACTION: Notice.

SUMMARY: This notice describes the role of NIH in relation to biotechnology.

FOR FURTHER INFORMATION CONTACT: Additional information can be obtained from Dr. William J. Gartland, Office of Recombinant DNA Activities, Building 31, Room 3B10, National Institutes of Health, Bethesda, Maryland 20892, (301) 496-6051.

SUPPLEMENTARY INFORMATION: The primary role of the National Institutes of Health (NIH) in relation to biotechnology has been the funding of basic biomedical research. This is discussed in a February, 1985, NIH Report on Biotechnology prepared for the Committee on Appropriations, U.S. House of Representatives, which describes NIH-supported basic research both "directly related to or utilizing the new biotechnology" and "underlying the new biotechnology." The NIH will continue its extensive support of basic biomedical research which can be expected to lead both to many future advances in biotechnology, and to uses of biotechnology towards the better understanding, diagnosis, prevention, and treatment of human diseases.

In addition, the NIH was the first Federal agency involved in the oversight of the safety of recombinant DNA research; NIH's role is described in detail in the NIH Guidelines for Research Involving Recombinant DNA Molecules (Guidelines). The Guidelines were first published in 1976 and have been revised many times since then. A complete revision of the Guidelines appeared in the **Federal Register** of November 23, 1984 (49 FR 46266–46291). A complete new republication appears in the **Federal Register** of May 7, 1986 (51 FR 16958). A summary of the contents of the Guidelines is given below. It is NIH's intention to continue to revise and oversee the Guidelines, and to continue the NIH Recombinant DNA Advisory Committee (RAC) and the NIH Office of Recombinant DNA Activities (ORDA), described below.

Summary of Contents of Guidelines

Section I of the Guidelines includes: The purpose of the Guidelines; definitions of terms used; and the statement that "the Guidelines are applicable to all recombinant DNA research within the United States or its territories which is conducted at or sponsored by an Institution that receives any support for recombinant DNA research from the National Institutes of Health."

Section II of the Guidelines gives a general discussion of "physical containment" and "biological containment."

Section III of the Guidelines divides recombinant DNA experiments into four classes, i.e. "III–A. Experiments which require specific RAC review and NIH and IBC [institutional biosafety committee] approval before initiation of the experiment; III–B Experiments which require IBC approval before initiation of the experiment; III–C. Experiments which require IBC notification at the time of initiation of the experiment; [and] III–D. Experiments which are exempt from the procedures of the Guidelines." For class III–A, it is specified that "Experiments in this category cannot be initiated without submission of relevant information on the proposed experiment to NIH, the publication of the proposal in the **Federal Register** for thirty days of comment, review by the RAC, and specific approval by NIH." Four types of experiments are placed within Class III–A, i.e.: "III–A–1. Deliberate formation of recombinant DNAs containing genes for the biosynthesis of toxic molecules lethal for vertebrates at an LD_{50} of less than 100 nanograms per kilogram body weight. . . .; III–A–2. Deliberate release into the environment of any organisms containing recombinant DNA. . . .; III–A–3. Deliberate transfer of a drug resistance trait to microorganisms. . . .; [and] III–A–4. Deliberate transfer of recombinant DNA or DNA derived from recombinant DNA into human subjects. . . ."

Section IV of the Guidelines specifies the roles and responsibilities of "each institution conducting or sponsoring recombinant DNA research covered by these Guidelines" including the Institutional Biosafety Committee, Biological Safety Officer, and Principal Investigator. Noncompliance with the Guidelines may result in "suspension, limitation or termination of financial assistance for such projects and of NIH funds for other recombinant DNA research at the Institution. . . ." Section IV of the Guidelines also discusses the roles and responsibilities of the NIH, including the Director, NIH, the NIH Recombinant DNA Advisory Committee (RAC), and the NIH Office of Recombinant DNA Activities (ORDA). The RAC "shall consist of 25 members . . . appointed by the [HHS] Secretary or designee, at least fourteen of whom shall be selected from authorities knowledgeable in . . . scientific fields . . . and at least six of whom shall be persons knowledgeable in applicable law, standards of professional conduct and practice, public attitudes, the environment, public health, occupational health, or related fields. Representatives from Federal agencies shall serve as non-voting members." No changes in the Guidelines shall be made without publication of the proposed change for public comment in the **Federal Register** at least 30 days prior to a RAC meeting, and consideration by the RAC.

Section V of the Guidelines contains footnotes and references for Sections I-IV.

Section VI of the Guidelines, entitled "Voluntary Compliance," states that "individuals, corporations, and

institutions not otherwise covered by the Guidelines are encouraged to do so. . . . Since commercial organizations have special concerns, such as protection of proprietary data, some modifications and explanations of the procedures . . . are provided."

Appendix A and Appendix C of the Guidelines list certain types of experiments which are exempt from the Guidelines. Appendix B classifies disease-causing microorganisms. Appendix D describes certain action taken under the Guidelines. Appendix E describes certified host-vector systems. Appendix F gives containment conditions of cloning of genes coding for the biosynthesis of molecules toxic for vertebrates. Appendix G describes physical containment and defines four Biosafety Levels (BL1, BL2, BL3, and BL4). Appendix H covers shipment of organisms containing recombinant DNA molecules. Appendix I discusses biological containment. Appendix J describes the Biotechnology Science Coordinating Committee. Appendix K gives physical containment for large-scale uses of organisms containing recombinant DNA molecules. Appendix L specifies conditions under which certain plants may be approved for release into the environment.

November 22, 1985, Revision of the Guidelines

On November 22, 1965, a number of revisions of the Guidelines were promulgated in the **Federal Register** (50 FR 48344). One of these changes added a new sentence at the end of Section III-A of the Guidelines which specifies that if experiments in the category that require RAC review and NIH and IBC approval before initiation "are submitted for review to another Federal agency, the submitter shall notify ORDA; ORDA may then determine that such review serves the same purpose, and based on that determination, notify the submitter that no RAC review will take place, no NIH approval is necessary, and the experiment may proceed upon approval from the other Federal Agency." It is NIH's intention to consider such experiments (including "deliberate release") on a case-by-case basis. In many such cases, including submissions to the Environmental Protection Agency or the Department of Agriculture, the NIH may well decide "that no RAC review will take place, no NIH approval is necessary, the experiment may proceed upon approval from the other Federal Agency."

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Part III

Department of Agriculture

Animal and Plant Health Inspection Service

7 CFR Parts 330 and 340

Plant Pests; Introduction of Organisms and Products Altered or Produced Through Genetic Engineering; Proposed Rule and Notice of Public Hearings

Advanced Notice of Proposed Guidelines for Biotechnology Research

DEPARTMENT OF AGRICULTURE

Animal and Plant Health Inspection Service

[Docket No. 85-351]

7 CFR Parts 330 and 340

Introduction of Organisms and Products Altered or Produced Through Genetic Engineering Which Are Plant Pests or Which There is Reason to Believe Are Plant Pests

AGENCY: Animal and Plant Health Inspection Service, USDA.

ACTION: Proposed rule and notice of public hearings.

SUMMARY: This document proposes to establish regulations for the introduction (importation, interstate movement, or release into the environment) of genetically engineered organisms or products which are plant pests or which there is reason to believe are plant pests (regulated articles). The proposed regulations set forth the procedures for obtaining a permit which would be required prior to a regulated article being moved into or through the United States, moved interstate, or released into the environment. These regulations are necessary to prevent the introduction into and dissemination and establishment of plant pests in the United States.

This document also gives notice of public hearings concerning this proposal.

DATES: Written comments concerning this proposed rule must be received on or before August 25, 1986. Public hearings will be held on July 29, 1986, in Sacramento, California; and on August 5, 1986, in Washington DC.

ADDRESSES: Written comments should be submitted to Dr. James W. Glosser, Associate Administrator, Animal and Plant Health Inspection Service, U.S. Department of Agriculture, Room 313E, Administration Building, 14th and Independence Avenue SW., Washington, DC 20250. Comments should state that they are in response to Docket Number 85-351. Written comments received may be inspected in Room 313-E of the Administration Building between 8 a.m. and 4:30 p.m., Monday through Friday, except holidays. The public hearings will be held at the following locations: (1) On July 29, 1986, at Sacramento Convention Center, Yuba Room, 1100 14th St., Sacramento, California 95814, and (2) on August 5, 1986, at Jefferson Auditorium, South Agriculture Building, 14th and Independence Ave. SW., Washington, DC 20250.

FOR FURTHER INFORMATION CONTACT: John R. Wood, Director, Biotechnology and Environmental Coordination Staff, Animal and Plant Health Inspection Service, U.S. Department of Agriculture, Room 600, Federal Building, 6505 Belcrest Road, Hyattsville, MD 20782, 301-436-8896.

SUPPLEMENTARY INFORMATION:

Public Hearings

A representative of the Animal and Plant Health Inspection Service will present a statement concerning the proposed regulations at each of the public hearings described under **"ADDRESSES."** Any interested person may appear and be heard in person, by attorney, or by other representative.

Each hearing will begin at 9:30 a.m. and is scheduled to end at 5 p.m., local time. However, a hearing may be terminated at any time after it begins if all of those persons at the hearing who desire an opportunity to speak have been heard. Persons who wish to speak are requested to register with the presiding officer prior to the hearing at the location of the hearing from 8:30 a.m. to 9:30 a.m. Those persons registered will be heard in the order of their registration. However, any other person who wishes to speak at the hearing will be afforded such opportunity after the registered persons have been heard. It is requested that two copies of any written statements that are presented be provided to the presiding officer at the hearing. If the number of preregistered persons and other participants in attendance at the hearing warrants it, the presiding officer may limit the time for each presentation in order to allow everyone wishing to speak the opportunity to be heard.

Background

On December 31, 1984, as a part of the Office of Science and Technology Policy's Proposal for a "Coordinated Framework for Regulation of Biotechnology" (49 FR 50856-50907), the U.S. Department of Agriculture (USDA) published a statement of policy for the regulation of biotechnology processes and products (49 FR 50897-50904). USDA's policy statement was not an exhaustive set of application requirements, but a document intended to inform the public, scientists, and industry of USDA's perspective on the regulation of biotechnology processes and products. That perspective, simply stated, was that USDA anticipates that agriculture and forestry products developed by modern biotechnology will not differ fundamentally from conventional products.

USDA indicated in the policy statement that while its existing regulatory framework is adequate, it would constantly reevaluate its regulatory position as the state of the art of biotechnology evolves. The policy statement also indicated that "USDA will use a formal and logical process to ensure the continual integration of safety concepts and other principles for the evaluation of biotechnological processes and products in agriculture and forestry for licensing and granting of permits. Should any new processes or products be shown to require additional regulatory measures, USDA will amend regulations or will request additional authority." (49 FR 50904).

USDA's mandate is to protect and enhance agriculture and forestry in the United States. USDA is confident that organisms altered or produced through genetic engineering will play a major role in increased plant yield and improved plant quality. However, such organisms may also present a risk of plant pest introduction.

During the last 10 years, there has been a dramatic increase in biotechnological research and product development throughout the world. For example, the manipulation or movement of genetic material by recombinant DNA technology has made its possible to perform genetic engineering procedures with an increasing number of applications in agriculture and forestry (see 49 FR 50899-50900). There is also a growing domestic and international trade in genetically engineered organisms. Such trade may introduce exotic plant diseases and pests into the United States and pose a threat to U.S. agriculture if the introduction and dissemination of certain genetically engineered organisms is not regulated. Certain organisms themselves, the cultures in which they are transported, or their packaging may be contaminated with plant pests. It is necessary, therefore, to establish regulatory control over genetically engineered organisms which are plant pests or which there is reason to believe are plant pests. Other genetically engineered organisms, which are engineered from certain organisms which are not plant pests or classified in taxa which do not contain plant pests, need not be regulated.

Regulation of the Introduction of Organisms and Products Altered or Produced Through Genetic Engineering Which Are Plant Pests or Which There is Reason to Believe Are Plant Pests

This document proposes to establish a new part entitled, "Introduction of Organisms and Products Altered or

Produced Through Genetic Engineering Which Are or Which There is Reason to Believe Are Plant Pests" in Title 7 of the Code of Federal Regulations (7 CFR) (hereinafter referred to as the proposed regulations), pursuant to the authority of the Federal Plant Pest Act of May 23, 1957, as amended, (FPPA), (7 U.S.C. 150aa–150jj) and the Plant Quarantine Act of August 20, 1912, as amended (PQA), (7 U.S.C. 151, 164, 166, 167). The regulations propose to regulate the introduction (importation, interstate movement, and release into the environment) of certain organisms or products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests. These articles would be regulated in order to prevent the introduction, spread, or establishment of plant pests that are new to or not known to be widely prevalent or distributed within and throughout the United States. (See 7 U.S.C. 150dd(a)).

The PQA and the FPPA provide authority for regulating plant pests and other articles. Specifically, the PQA provides authority to regulate the importation and interstate movement of plants and plant products that may result in the entry into the United States of injurious plant diseases or insect pests. The FPPA authorizes the issuance of regulations to prevent the dissemination into the United States or interstate of plant pests, in any situation in which such regulations are not authorized under the Plant Quarantine Act. These provisions include authority for regulating the "release into the environment" in the United States of certain genetically engineered organisms.

"Release into the environment" would be defined to mean "the use of a regulated article outside the constraints of physical confinement that are found in a laboratory, contained greenhouse, or a fermenter or other contained structure."

The proposed regulations which are designed to prevent the release into the environment of genetically engineered organisms which are plant pests or for which there is reason to believe are plant pests are consistent with the legislative intent of the FPPA which gave USDA the authority to regulate plant pests and other articles in order to prevent injury and damage to plants, plant products, and crops.

The FPPA was enacted in 1957 and was intended as gap filling legislation, for the purpose of protecting American agriculture against invasion by foreign plant pests and diseases, which are "new to or not theretofore known to be widely prevalent or distributed within and throughout the United States". The FPPA was enacted because of deficiencies in such acts as the Insect Pest Act (repealed), the Plant Quarantine Act (7 U.S.C. 151 *et seq.*) the Mexican Border Act (7 U.S.C. 149) and the Mollusk Act (repealed), (See Report No. 289 to accompany H.R. 3476, 85th Congress, 1st Session, pp. 2–3).

USDA believes that when a regulated article is released into the environment from a contained greenhouse, a laboratory, or any other containment facility, such release is tantamount to the introduction of an organism which is "new to and not theretofore known to be widely prevalent or distributed within and throughout the United States" and which there is reason to believe is a plant pest. Such exotic organisms are subject to regulation under the FPPA.

Restrictions on the introduction of regulated articles (§ 340.0)

The proposed regulations restrict the "introduction" of those organisms and products altered or produced through genetic engineering which are a plant pest or for which there is reason to believe are plant pests. Such organisms are referred to as "regulated articles".

Modern genetic engineering techniques permit genetic material to be intentionally combined in organisms in combinations that occur only at low frequency in nature. These traits may be new to the organism, or new to the environment in which the organism is released. Some of these genetically engineered organisms may exhibit new or altered traits affecting, for example, their survivability, host range, substrate utilization, or competition. Such organisms may be plant pests.

The most significant concern to USDA from a regulatory viewpoint is when an organism or product is altered or produced by genetic engineering and one or more of its constituents (donor, vector/vector agent or recipient) comes from a family or genus of organisms known to contain plant pests. USDA believes that such a genetically engineered organism needs to be regulated. This is because when an organism whose constituents come from a group of organisms that are plant pests, there is a risk that certain undesirable traits may be transferred to the new organism and may survive when the organism is released into the environment. The introduction of such organisms would be prohibited unless authorized by a permit.

Section 340.0(a) prohibits any person from introducing a regulated article unless the introduction is authorized by a permit and such introduction is in conformance with all of the applicable restrictions contained in Part 340.

Section 340.0(b) provides that if any regulated article is not in compliance with the requirements of Part 340 when introduced, that such regulated article shall be subject to the immediate application of remedial measures or safeguards against escape of the article as the inspector determines is necessary to prevent the introduction of plant pests.

For informational purposes footnote 1 has been included to inform persons that the introduction into the United States of organisms that have been altered or produced through genetic engineering may be subject to other regulations that have been promulgated under the Federal Plant Pest Act (7 U.S.C. 150aa *et seq.*), the Plant Quarantine Act (7 U.S.C. 151 *et seq.*), and the Federal Noxious Weed Act U.S.C. 2801 *et seq.*) which are found in 7 CFR Parts 319, 321, 330, and 360.

Proposed Part 340 would be applicable to the introduction of organisms or products altered or produced through genetic engineering whose plant pest status is uncertain and would not affect the Department's existing regulations in 7 CFR 330.200 entitled, "Subpart—Movement of Plant Pests." The regulations in 7 CFR 330.200 specify permit requirements for the importation and interstate movement of "known" plant pests which are naturally occurring and have not been genetically engineered, where there is no uncertainty as to their plant pest status.

Thus, a person seeking to import or move interstate the fungal organism *Puccinia horiana*, the cause of Chrysantheum white rust disease, would be subject to the regulations in 7 CFR 330.200. However, if the fungus *P. horiana* was used as either the donor or recipient organism to genetically engineer a new type of organism, the genetically engineered organism would be subject to regulation under proposed Part 340.

In order to reflect the distinctions between the plant pest regulations in §§ 330.200–330.212 and the proposed regulations, USDA is amending the definition of "plant pest" in 7 CFR 330.100 to indicate that the regulations in §§ 330.200–330.212 are not applicable to plant pests that have been genetically engineered.

Footnote 2 has also been included for informational purposes. This footnote explains the authority available to USDA to take emergency action against a regulated article by seizing, destroying, quarantining, or disposing of any regulated article which is a plant

pest or is believed to be infested or infected by or otherwise believed to contain a plant pest.

Definitions (§ 340.1)

In addition to the definitions of "introduction" and "release into the environment" the proposed regulations in § 340.1 present definitions of the following terms: "Certificate of exemption", "Classical genetics", "Deputy Administrator", "Donor organism", "Environment", "Genetic engineering", "Genetic manipulation", "Inspector", "Interstate", "Move", "Mutagen", "Organism", "Pathogen", "Permit", "Person", "Plant", "Plant pest", "Plant Protection and Quarantine", "Product", "Recipient organism", "Regulated article", "Responsible person", "Secretary", "State", "United States", and "Vector or vector agent", "Well-characterized and contains only non-coding regulatory regions".

Genetic engineering is defined as "genetic manipulation of organisms by procedures other than those used in classical genetics, including, but not limited to, protoplasts, cell, and embryo fusions; recombinant DNA engineering, and directed mutagenesis."

In order to explain the meaning of certain terms in the definition of genetic engineering in the proposed regulations, the following words are defined further in the proposed regulations:

Organism is defined to mean "any active, infective, or dormant stage or life form of an entity characterized as living, including vertebrate and invertebrate animals, plants, bacteria, fungi, mycoplasmas, mycoplasma like organisms, as well as viroids, viruses, and prions, or any entity related to the foregoing and any part, copy, or analog thereof, including deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) which is infectious."

The meaning of the term "organism(s)" encompasses not only whole organisms, but also portions of organisms (e.g., organs, organelles or portions of organelles, segments of DNA or RNA, etc.), analogs of organisms (functionally similar to the organism but not necessarily an exact copy of the organism or part of the organism), and natural or synthetic copies of organisms or portions of organisms if any confer infectivity. An organism may be in a stage or form ordinarily known of as "living." Such a living organism may be "dormant" or it may be "active." Some organisms, such as viruses, viroids, and prions, are considered by some people to be living (as in "active"), and by other people not to be alive. For the purposes of the proposed regulations, these organisms, portions of natural or synthetic DNA and RNA, and similar organisms, are considered to be active or infectious (capable of entering into functioning, or integrating themselves into other organisms and affecting the functioning of the other organism). Inactivated or dead organisms, or portions of these organisms, are covered under this definition because they may be active or infectious in that they are capable of functioning or affecting the functioning of another organism.

Classical genetics is defined as "genetic manipulation of organisms by procedures which occur in nature or in conventional breeding, including but not restricted to such methods as natural and hand pollination, and natural and artificial insemination and undirected mutagenesis."

Genetic manipulation is defined as "the process of causing hereditary variation in an organism through the introduction of change in its DNA and RNA structure or function."

Mutagens are defined as "agents such as colchicine, radioactive elements, lasers, and ultraviolet light that cause mutations without the exchange of genetic material between organisms."

The proposed regulations define a plant as "any living stage or form of any organism of the plant kindgom including, but not limited to, bacteria, prokaryotic algae, eukaryotic algae, fungi, mosses, club mosses, ferns, horsetails, liverworts, angiosperms, gymnosperms, and lichens (which contain algae) including any parts (e.g., pollen, seeds, cells, tubers, stems) thereof, and any cellular components (e.g., plasmids, ribosomes, etc.) thereof."

Plant pest is defined as "any living stage (including active and dormant forms) of insects, mites, nematodes, slugs, snails, protozoa, or other invertebrate animals; bacteria, fungi, other parasitic plants or reproductive parts thereof viruses or any organisms similar to or allied with any of the foregoing; or any infectious agents or substances, which can directly or indirectly injure or cause disease or damage in or to any plant or parts thereof, or any processed, manufactured, or other products of plants."

The proposed regulations also present a definition of the term "Responsible person." Responsible person is defined as the person who has control and will maintain control over the introduction of the regulated article and assure that all conditions contained in the permit and requirements in this part are complied with. A responsible person shall be a resident of the United States or shall designate an agent who is a resident of the United States.

Under the proposed regulations a regulated article is defined as "any organism or any product which has been altered or produced through genetic engineering, if the donor organism, recipient organism, or vector or vector agent belongs to a group designated in § 340.2 of this part, or any organism or product altered or produced through genetic engineering which the Deputy Administrator determines is a plant pest or has reason to believe is a plant pest.

Excluded are microorganisms that are non-pathogenic, non-infectious, and otherwise not a plant pest, that have resulted from the addition of genetic material that is well characterized and contains only non-coding regulatory regions such as operators, promoters, origins of replication, terminators, and ribosome binding regions."

Under the proposed definitions the term "well characterized and contains only non coding regulatory regions" (i.e. operators, promoters, origins of replication, terminators, and ribosome binding regions) means the genetic material added to a microorganism in which the following can be documented about such genetic material:

a. The exact nucleotide base sequence of the regulatory region and any inserted flanking nucleotides;

b. The regulatory region and any inserted flanking nucleotides do not code for protein or peptide; and

c. The regulatory region solely controls the activity of other sequences that code for protein or peptide molecules or act as recognition sites for the initiation of nucleic acid or protein synthesis."

The definition of regulated article excludes recipient microorganisms that are non-pathogenic, non-infectious, and otherwise not a plant pest, that have resulted from the addition of genetic material that is well characterized and contains only non-coding regulatory regions.

The addition of the genetic material that is well characterized and which contains only non-coding regulatory regions has no coding capacity for the production of any gene product (proteins or peptides) and does not promote the production of any new material. These regulatory regions (operators, promoters, origins of replication, terminators, and ribosome binding sites) are responsible for the initiation and modulation of nucleic acid synthesis at the specific region where they appear in the chromosome. Thus, if the recipient microorganism is non-pathogenic, non-infectious, and otherwise not a plant pest, then the resulting genetically engineered microorganism would be

non-pathogenic, non-infectious, and otherwise not a plant pest.

The exclusion from regulation of certain genetically engineered microorganisms that have resulted from the addition of genetic material that is well-characterized and contains only noncoding regulatory regions such as operators, promoters, origins of replication, terminators and ribosome binding regions was adopted by the Biotechnology Science Coordinating Committee of the Office of Science and Technology Policy.

In view of the above, USDA does not have reason to believe that such microorganisms are plant pests nor will they become plant pests.

The proposed regulations also contain a definition of pathogen. As used in the term "regulated article" pathogen means "a virus or microorganism (including its viruses and plasmids, if any) that has the ability to cause disease in other living organisms. Excluded are those microorganisms for which it can be documented that the microorganisms come from nonpathogenic species, (e.g. *Bacillus subtilis, Lactobacillus acidophilus,* and *Saccharomyces* species) or come from a nonpathogenic strain of a pathogenic species (e.g., *Escherichia coli* K–12)."

Like the definition of regulated article, the definition of pathogen references certain exclusions. A microorganism will not be deemed a pathogen if it can be documented that it comes from a nonpathogenic species (e.g., *Bacillus subtilis, Lactobacillus acidophilus,* or *Saccharomyces* species) or from a nonpathogenic strain of a pathogenic species (e.g. *Escherichia coli,* K–12).

Groups of organisms which are or contain plant pests (§ 340.2)

Proposed § 340.2 entitled, "Groups of organisms which are or contain plant pests" in a key provision in determining whether a genetically engineered organism is subject to regulation under this part. A person who has genetically engineered an organism intended for introduction should consult § 340.2 of the proposed regulations in order to determine if such organism is a "regulated article".

USDA is proposing to regulate only genetically engineered organisms or products which are plant pests or for which there is reason to believe are plant pests, and not to regulate an organism or product merely because of the process by which it was produced. USDA believes that an organism or product is a plant pest if the donor, recipient, vector or vector agent of the genetically engineered organism or product comes from a member of one of the groups listed in § 340.2.

USDA further believes that a genetically engineered organism or product should be designated as a "regulated article" when, based on experience, the Deputy Administrator determines that the organism or product is a plant pest or has reason to believe it is a plant pest.

Basis for Listing Organisms in § 340.2

The list of organisms in § 340.2 was developed based on previous experience with issuing plant pest permits for organisms not altered by genetic engineering. For the past several decades, the Department has been issuing from 1,000 to 3,000 plant pest permits per year for scientific or experimental purposes. This experience, coupled with pest reports from the USA and other countries, and consultation with pathologists, mycologists, nematologists, entomologists, botanists, and other scientists from the Department, has been consolidated into the list in § 340.2 of organisms from a family or genus or organisms known to contain plant pests. The purpose of § 340.2 is to indicate those organisms that are known plant pests or considered potential plant pests.

Section 340.2 does not attempt to list every pest species. That would be impossible. Not only because hundred of thousands of species are involved, but also because within species some subgroups may be pests and other subgroups may not be pests. Also, the pest status of many species is unknown. Section 340.2 lists higher taxa (taxonomic groups) which include known pest species or species for which the Department has reason to believe are pest species.

The taxonomic scheme used in § 340.2 is that of S.P. Parker, *Synopsis and Classification of Living Organisms,* McGraw Hill (1984). This is a five-kingdom system. For most taxa, common names are given merely for convenience of the user. Reliance should be placed upon the Latin scientific names. However, for certain groups, such as viroids, plant viruses, mycoplasma like organisms associated with plants and prions, in which there are no Latin names, the accepted common names are given. Section 340.2 covers all organisms, including donors, vectors, and recipients that may be used in proposed biotechnology projects. Within each taxon, all species are subject to review by the Department, unless there are taxa of lower rank specifically listed, in which instance, only those specifically listed are considered to be plant pests or potential plants pests, and other classified organisms not listed are considered not to be plant pests or potential plant pests.

A number of groups of organisms (particularly microorganisms) were unknown until recent years. Examples are groups such as fungi, bacteria, viruses, viroids, rickettsia, mycoplasma, mycoplasma-like organisms, spirochetes, etc. In every group, a significant number of plant pests are now known. USDA has reason to believe that groups of organisms which are currently unclassified or unknown are likely to contain plant pests, and, therefore, are included in § 340.2.

USDA has also included all viroids and prions on the list of organisms which are or contain plant pests. All viroids and prions known at this time are pathogens. Presently known viroids are pathogenic to plants; the two diseases known to be caused by prions occur in animals. These organisms are difficult to work with and have not been isolated in "pure culture"; they are still under intensive investigation in an effort to learn about the organisms themselves, the diseases they cause, their pathogensis, the genetic mechanisms responsible for their replication, defenses against these organisms, methods for detection, etc. In view of the fact that so little is known about these two groups of infectious "organisms", which are composed, so far as is now known, of naked RNA and protein (viroids) and apparently of protein alone (prions), it is reasonable to include organisms modified through the use of viroids and prions as regulated articles. Thus, prions and viroids are included in § 340.2.

Permits (§ 340.3)

Proposed § 340.3(a) explains that a written application for a permit should be submitted by the responsible person at least 180 days in advance of the proposed introduction by submitting an application form that has been obtained from Plant Protection and Quarantine.

For informational purposes footnote 3 has been added to advise persons that applications for a permit are available from the Biological Assessment Support Staff, Plant Protection and Quarantine, Animal and Plant Health Inspection Service, U.S. Department of Agriculture, Federal Building, 6505 Belcrest Road, Hyattsville, MD 20782, or from local offices of the Animal and Plant Health Inspection Service which are listed in telephone directories.

An application for a permit would require the submission of data to USDA needed to assess the risk to argiculture in the United States, when certain

organisms which have been modified or altered through genetic engineering are introduced. The following discussion explains the rationale for requiring that certain data be submitted in an application for a permit.

Proposed § 340.3(a)(2) requires the submission of data concerning the scientific, common, and trade names and all designations necessary to identify the donor organism, recipient organism, vector or vector agent of each regulated article which is a product, and for the regulated article. Such data would be used by USDA in identifying the constituents of the regulated article in order to determine the plant pest status of the regulated article.

Under proposed § 340.3(a)(3) the name and address of the person(s) who developed and/or supplied the regulated article would be used by USDA if additional information was needed concerning the origin and process used to create the regulated article.

Information required under proposed § 340.3(a)(4) concerning the method of movement of the regulated article is needed so that Plant Protection and Quarantine inspectors can anticipate the arrival of the regulated article and ensure that such article is properly inspected.

Data that is required under proposed § 340.3(a) (5) through (8) concerning a detailed description of the anticipated or actual expression of the genetic material in the regulated article and its characteristics; a description of the molecular biology used to produce the regulated article; the country of origin where the donor, recipient, vector or vector agent and regulated article were collected, developed and produced; and a detailed description of the purpose for the introduction, including a detailed description of the proposed experimental and/or production design, would provide Plant Protection and Quarantine with the data necessary to make a determination of the potential plant pest risk and whether a permit could be issued for the regulated article.

Data that is required by proposed § 340.3(a)(9), (11, (12) and (14) concerning the quantity of the regulated article to be introduced and proposed schedule of introductions; a detailed description of the intended destination and distribution of the regulated article; a detailed description of the proposed procedures, processes and safeguards which will be used to prevent escape and dissemination of the regulated article at each intended destination; and a detailed description of the proposed method of final disposition of the regulated article would be used along with the other data that would have to be submitted in a application, to assess the potential environmental impact of issuing a permit.

Data required by proposed § 340.3(a)(10) (a detailed description of the processes, procedures, and safeguards which have or will be used in the United States or in the country of origin to prevent contamination, release, and dissemination and that were used in the production of the donor and recipient organism, vector or vector agent, constituent of each regulated article which is a product, and the regulated article) would be needed to assess the purity of the regulated article. Data required by proposed § 340.3(a)(13) concerning any biological material that may accompany the regulated article during movement is necessary to assess both the purity of the regulated article as well as whether any additional containment safeguards would be necessary, as a condition of introduction.

Proposed § 340.3(b) explains the administrative action that will be taken on an application for a permit submitted pursuant to § 340.3(a).

Under proposed § 340.3(b) upon receipt and review by Plant Protection and Quarantine of an application for a permit, a permit shall be granted or denied. If a permit is denied the responsible person shall be promptly informed of the reasons why the permit was denied. If a permit is granted, the permit will specify the applicable conditions for the introduction of the regulated article.

Proposed § 340.3(c) lists the standard conditions which shall be listed on the permit and which are applicable to the introduction of regulated articles. In addition to the standard conditions, the Deputy Administrator may list supplemental conditions which are applicable to the introduction of a particular regulated article for which a permit has been granted.

The proposed standard conditions to be listed on the permit are:

(1) The regulated article shall be maintained and disposed of (when necessary) in a manner determined necessary by the Deputy Administrator;

(2) All packing material, shipping containers, and any other material accompanying the regulated article shall be treated or disposed of as determined necessary by the Deputy Administrator;

(3) The regulated article shall be kept separate from other organisms, except as specifically allowed in the permit;

(4) The regulated article shall be maintained only in areas and premises specified in the permit;

(5) An inspector shall be allowed access, during regular business hours to the place where the regulated article is maintained;

(6) The regulated article shall, when possible, be kept identified with the label showing the name of the regulated article, and when applicable, the port accession number and date of importation;

(7) The regulated article shall be subject to the application of measures determined by the Deputy Administrator to be necessary to prevent the accidental or unauthorized release of the regulated article;

(8) The regulated article shall be subject to the application of remedical measures (including disposal) determined by the Deputy Administrator to be necessary to prevent the spread of plant pests;

(9) A person who has been issued a permit shall submit to Plant Protection and Quarantine monitoring reports on the performance characteristics of the regulated article, as deemed necessary by the Deputy Administrator;

(10) Plant Protection and Quarantine shall be orally notified immediately, and in writing, within the time periods specified below, in the event of the following ocurrences:

(i) Within 24 hours in the event of any accidental or unauthorized release of the regulated article;

(ii) Within 5 working days if the regulated article is found to have characteristics substantially different from those listed in the application for a permit; and

(iii) Within 5 working days if the regulated article dies.

(11) A permittee or his/her agent who seeks to import a regulated article into the United States shall:

(i) Import or offer the regulated article for entry only at a port of entry which is designated by an asterisk in 7 CFR 319.37–14(b);

(ii) Notify Plant Protection and Quarantine promptly upon arrival of any regulated article at a port of entry, of its arrival by such means as a manifest, customs entry document, commercial invoice, waybill, a broker's document, or a notice form provided for such purpose; and

(iii) Mark and identify the regulated article in accordance with § 340.6 of this part.

The provisions in proposed § 340.3(c) (1) through (4) pertaining to the disposal of regulated articles, treatment and disposal of shipping containers and packing material, segregation and maintenance of regulated articles are necessary to prevent the dissemination and establishment of plant pests.

The proposed provisions in § 340.3(c)(5) and (6) which pertain to allowing an inspector access to the location where the regulated article is maintained as well as keeping the regulated article properly identified is necessary to enable an inspector to make a determination that the conditions of this part are being complied with and to ensure that a regulated article can be properly identified at the site where it is maintained.

The proposed provisions in § 340.3(c)(7) and (8) which provide that a regulated article shall be subject to the application of measures determined by the Deputy Administrator to be necessary to prevent the accidental or unauthorized release of the regulated article, as well as the regulated article being subject to the application of remedial measures necessary to prevent the spread of plant pests, are necessary to prevent the possible dissemination and establishment of plant pests.

Under proposed § 340.3(c)(9) it is necessary to require that a person who has been issued a permit submit monitoring reports on the characteristics of the regulated article, as deemed necessary by the Deputy Administrator in order for Plant Protection and Quarantine, under certain circumstances to make a final determination on the plant pest status of the regulated article.

The reporting requirements in proposed § 340.3(c)(10) are necessary for Plant Protection and Quarantine to take remedial action in the event of an accidental or unauthorized release, or in the event that the regulated article exhibits substantially different characteristics from what was described in an application, or in the event the regulated article dies to determine if the regulated article is a plant pest or was infested or infected by a plant pest.

The provisions in proposed § 340.3(c)(11) pertaining to importation at certain ports of entry designated in 7 CFR 319.37–14(b) are necessary to ensure that regulated articles are imported only at those ports where there are specially trained personnel and treatment facilities in order to prevent the introduction of plant pests that may accompany or be in the regulated article. The arrival notification and marking and identity provisions would assure that Plant Protection and Quarantine is adequately notified in writing of the arrival of such regulated articles and that the articles can be expeditiously processed and identified after such notification at the port of entry.

Proposed § 340.3(d) contains the provisions under which a permit may be withdrawn by the Deputy Administrator or an inspector if a determination is made by him that the holder of the permit has not complied with one or more of the conditions listed on the permit. This subsection provides that the reason for withdrawal of the permit shall be confirmed in writing as promptly as circumstances allow and that the withdrawal may be appealed in writing to the Deputy Administrator within ten (10) days after receiving the written notification of the withdrawal. These provisions set forth due process requirements pertaining to the withdrawal of a permit.

Certificate of exemption (§ 340.4)

Proposed § 340.4 discusses the provisions for the issuance of a certificate of exemption.

Proposed § 340.4(a) provides that the Deputy Administrator may issue a certificate of exemption for the introduction of organisms which have been modified through genetic engineering, but which are not subject to regulation under this part, when the introduction of such organisms might otherwise be impeded because of the similarity of the nonregulated organism to other organisms which are subject to regulation under Part 340.

Thus, a person seeking to introduce a nonregulated organism which has been altered or modified through genetic engineering may wish to apply for a certificate of exemption prior to such introduction in order to facilitate easy introduction of the organism. Such a certificate will establish that the organism is not subject to regulation under Part 340.

Proposed § 340.4(b) explains the procedure for requesting a certificate of exemption. To obtain a certificate of exemption a person should submit an application form which has been obtained from Plant Protection and Quarantine, which contains data required by § 340.3(a) (1), (2), and (5) and should indicate that such data is being submitted as a request for a certificate of exemption. A person should also submit a statement indicating why he or she believes the organism or product is not a plant pest.

Marking and identity (§ 340.5)

Proposed § 340.5 would require certain marking and identification information to be plainly and correctly borne at the time of importation on the outer container of a regulated article. In order to comply with specified requirements of the Plant Quarantine Act, any regulated article for importation, including any article for importation by mail, would be required to bear at the time of importation the general nature and quantity of the contents; the country and locality where collected, developed, manufactured, reared, cultivated, or cultured; the name and address of the shipper, owner, or person shipping or forwarding the article; and the name and address and telephone number of the consignee (in the case of mail the consignee would be Plant Protection and Quarantine).

A regulated article for importation other than by mail would be required to bear an identifying shipper's mark and number. This would enable an inspector to locate the regulated article at the port of entry by comparing the shipper's mark and number on available entry documents (e.g., manifest, waybill) with such information on the container.

Such regulated articles would also be required to bear the number of the written permit authorizing the importation, if one was issued. This would enable the inspector to check whether a valid permit was actually issued for the article in question.

The proposal would also require any regulated article for importation by mail to be mailed to Plant Protection and Quarantine at a port of entry designated by an asterisk in the list of ports of entry in 7 CFR 319.37–14(b). This appears to be necessary in order to prevent direct mailing to the intended recipient, and to ensure the requirements of the proposed part have been met, e.g., that the regulated article is properly marked and shipped in the proper containers. The proposal would further require a package containing a regulated article for importation by mail to contain within each package a sheet of paper bearing the name, address, and telephone number of the intended recipient. This would allow Plant Protection and Quarantine to be able to forward the package to the intended recipient. Also inclusion of the telephone number of the intended recipient for mailed articles would allow Plant Protection and Quarantine to contact the intended recipient for the purpose of obtaining any necessary clarifications for determining eligibility for importation of such articles. With respect to importation of articles other than by mail, this requirement is not necessary because the representative or agent of the intended recipient would be available at the port of entry to provide any necessary clarifications.

It is also proposed that shipments containing regulated articles be required to be accompanied by an invoice or packing list indicating the contents of the shipments. This appears necessary because such information on the outside of a package or on a regulated article

could be rendered illegible, destroyed, or lost because of handling during shipment. This requirement would not be an additional burden on importers since invoices and packing lists are required by the shipping industry and by the U.S. Customs Service.

Container requirements (§ 340.6)

Proposed § 340.6 specifies container requirements for the movement of regulated articles. Such requirements would be imposed to ensure that regulated articles do not inadvertently escape during the movement of the regulated article. The container requirements would be listed on a permit.

Proposed § 340.6(a) is a general provision which requires that a regulated article not be moved unless it complies with the specific container provisions of proposed § 340.6(b).

Proposed § 340.6(b) specifies the container requirements for the following types of regulated articles: plants and plant parts; seeds; live microorganisms and/or etiologic agents, cells, or subcellular elements; insects, mites, and related organisms; and other macroscopic organisms.

Under proposed § 340.6(b)(1) regulated articles which are plants and plant parts (except seeds, cells and subcellular elements) would have to be packed for transport in a sealed plastic bag of at least 5 mil thickness, inside a sturdy, sealed, leak-proof, outer shipping container constructed of corrugated fiberboard, corrugated cardboard, wood, or other material of equivalent strength. It is necessary to place the plastic bags in an outer shipping since plants and plant parts may be of a woody nature and could puncture the plastic packaging material. Such regulated articles need to be properly packaged to minimize the hazard ensuing from puncture and loss of contents during transport. Plastic bags of at least 5 mil thickness would not only contain the plants or plant parts, but should also maintain the plants or plant parts in a relatively healthy environment during the time it would take to ship them to their designation. Placing these bagged plants within a sturdy outer shipping container would further reduce the possibility of possible container puncture and release into the environment.

Under proposed § 340.6(b)(2) seeds would have to be transported in a sealed plastic bag of a least 5 mil thickness, inside a sealed metal container, which would be placed inside a second sealed metal container separated by shock absorbing cushioning material between the two containers. Each metal container would have to be independently capable of protecting the seed and preventing spillage or escape. The metal containers would then have to be enclosed in a sturdy outer shipping container constructed of corrugated fiberboard, corrugated cardboard, wood, or other material of equivalent strength. Certain seeds, especially seeds of parasitic plants, are so small (less than 2 millimeters in diameter) that they are especially susceptible to spillage, loss and dissemination into the environment unless extreme precautions are taken to ensure their enclosure. For this reason the system of sealed containers within an outer container would be required to be used for seeds which are regulated articles.

Proposed § 340.6(b)(3) provides container requirements for live microorganisms and/or etiologic agents, cells, or subcellular elements. The proposed container requirements for such articles are identical to the National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules. The requirements would be similar to the requirements for seeds (above), and would require the organisms to be in a sealed primary container, which would be placed in a secondary container separated by sufficient nonparticulate absorbent packing material to absorb the contents of the primary container. The secondary container would then be placed in a strong outershipping container (wood, corrugated carboard, or equivalent).

The preceding discussion regarding proposed § 340.6(b)(3) applies to volumes not exceeding 50 ml. This subsection also contains provisions for the shipment of volumes greater than 50 ml which are similar to the preceding requirements, and instructions for packing dry ice when it is used as a refrigerant.

Proposed § 340.6(b)(4) provides the container requirements for insects, mites, and related organisms. Such organisms may either be shipped in accordance with the proposed provisions for live microorganisms (referenced immediately above) or they could be transported in chilled escape proof primary containers within insulated secondary shipping containers all contained in an outer shipping container. This type of containerization provides for survival and reduced rate of normal functioning of the insects during transportation.

Proposed § 340.6(b)(5) provides the container requirements for microscopic organisms not covered in § 340.6(b)(1), (2), and (4) above. Microscopic organisms which do not require access to atmospheric oxygen could be contained in accordance with the requirements of §§ 340.6(b)(3) or 340.6(b)(4).

Those microscopic organisms that are not plants and that require continuous access to atmospheric oxygen would have to be placed in primary shipping containers constructed of a sturdy, crush-proof frame of wood, metal, or equivalent strength material surrounded by escape proof mesh or netting. Such primary shipping containers would then have to be placed in a similar secondary container and then within an outer shipping container. Such double enclosures would provide additional protection from escape, and an outer container with air holes would provide extra stability and resistance to puncture of the screening, as well as access to the amounts of air necessary for the survival of these larger organisms.

The container requirements for moving regulated articles appear adequate to prevent the escape and dissemination of regulated articles during movement.

For informational purposes footnote 4 has been added to indicate that the requirements of § 340.6 are in addition to and not in lieu of any other packing requirements such as those for the transportation of etiologic agents prescribed by the Department of Transportation in Title 49 of the Code of Federal Regulations or any other agency of the Federal government.

Costs and charges (§ 340.7)

Proposed § 340.7 relates to costs and charges in connection with the services of an inspector. It is the policy of Plant Protection and Quarantine that the services of an inspector during regularly assigned hours of duty and at the usual places of duty be furnished without cost to persons requiring inspection. Section 340.7 further provides that any costs or charges incidental to inspection, or compliance with the provisions of this part, other than an inspector's services, are not the responsibility of the Department of Agriculture. For informational purposes footnote 5 has been added to explain that the Department's provisions relating to overtime charges for an inspector services are set forth in 7 CFR Part 354.

USDA and EPA jurisdictional agreements pertaining to the review of microorganisms

Certain genetically engineered microorganisms that are intended for nonagricultural purposes, but are also plant pests (because they are pathogenic

to plants) will be regulated jointly by USDA under the FPPA and by the Environmental Protection Agency (EPA) under the Toxic Substances Control Act (TSCA). Such microorganisms may be used to enhance oil recovery, degrade pollutants, degrade paper pulp, or enhance artificial snow formation. Other genetically engineered microorganisms which are plant pests and are used as microbial pesticides would be regulated by USDA under the FPPA and by EPA under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA).

Pursuant to its statutory mandate under the FPPA, USDA shall review any genetically engineered microorganism that is a plant pest or where there is reason to believe that the microorganism is a plant pest. EPA has stated that certain genetically engineered microorganisms that are deemed "new organisms" shall be subject to review under TSCA. Thus, microorganisms deliberately formed from the genetic material of different genera (intergeneric microorganisms) will be reviewed by EPA under TSCA, and by USDA under the FPPA if it is a plant pest or there is reason to believe it is a plant pest. EPA and USDA will perform independent reviews, focusing on different objectives. In such instances, both agencies shall appoint contact persons who will coordinate the reviews, particularly to ensure data requests are not duplicated.

Genetically engineered microorganisms that are intergeneric in nature and are not or not believed to be or capable of becoming a plant pest shall be reviewed solely by EPA under TSCA unless a genetically engineered organism is intended for use as a pesticide, in which case it shall be reviewed solely by EPA under FIFRA. USDA shall review only if EPA determines in the course of its review that the microorganisms has plant pest qualities.

Genetically engineered microorganisms that are intrageneric in nature (formed from the same genera) that are plant pests or where there is reason to believe are plant pests shall be reviewed by USDA under the FPPA, regardless of whether the microorganism is intended for agricultural use. EPA shall also review the microorganism under TSCA if the microorganism is not intended to be used as a pesticide, if a pesticide it would be reviewed under FIFRA.

Genetically engineered microorganisms that are intrageneric in nature and are not plant pests or which there is no reason to believe are plant pests, and are not intended for use as a pesticide, shall be subject only to section 8(a) reporting requirements under TSCA. Because such microorganisms are not "new" organisms and since they are not believed to have plant pest qualities, such microorganisms are believed to present the least risk. EPA shall be responsible for informing USDA if it believes the microorganisms have plant pest qualities.

The preceding discussion on USDA and EPA reviews of genetically engineered microorganisms may be summarized as follows:

	Intergeneric	Intrageneric
Plant pest	USDA review and EPA review.	USDA review only, if intended for agricultural use; if nonagricultural use EPA reviews as well.
Non-plant pest.	EPA review only unless EPA review indicates presence of plant pests.	Neither agency reviews; EPA collects general information under section 8(a) of TSCA; EPA advises USDA of any potential plant pests.

Confidential Business Information

On September 23, 1985, a document was published in the **Federal Register** (50 FR 38561–38563) establishing the policy of the Animal and Plant Health Inspection Service (APHIS) for protecting certain privileged or confidential business information. The purpose of the policy statement was to establish minimum requirements to control and protect documents received by APHIS that in its judgment contain privileged or confidential business information as defined in IV–E of the policy statement concerning biotechnology and the Veterinary Biologics Program. Although the policy statement indicated that it would be applicable to biotechnology and the Veterinary Biologics Program, the APHIS policy is applicable to confidential business information received under any program within the agency.

The policy statement defined confidential business information (CBI) as information that would be protected from disclosure under section (b)(4) of the Freedom of Information Act (5 U.S.C. 552(b)(4). This includes trade secrets and commercial or financial information found to be confidential. The policy statement indicated that documents containing trade secrets and which the person submitting asserts are trade secrets will be deemed CBI. It was further indicated that documents containing commercial or financial information will be deemed confidential if review establishes that substantial competitive harm would result from disclosure. Persons desiring protection for confidential information must submit a detailed statement containing facts to show that the person faces active competition in the area to which the information relates, and that substantial competitive harm would result from disclosure.

In addition to the procedures described in its policy statement, APHIS shall follow the procedures described in Subpart A "Official Records" of Part 1 of Title 7 of the Code of Federal Regulations which set forth USDA's regulations for the disclosure of records under the Freedom of Information Act. (See 7 CFR 1.1–1.16).

Environmental Impacts

USDA's regulations implementing the National Environmental Policy Act (NEPA) are found in 7 CFR Part 1b and the APHIS Guidelines Concerning Implementation of NEPA Procedures were published in the **Federal Register** on August 28, 1979, and August 31, 1979, (See 44 FR 50381–50384 and 44 FR 51272–51274).

The issuance of all permits for the introduction of a genetically engineered organism would be in accordance with NEPA, the USDA regulations, and APHIS guidelines.

Emergency Authorities

USDA has emergency powers to prevent the introduction and dissemination of a genetically engineered organism which is a plant pest, pursuant to section 105 of the FPPA (7 U.S.C. 150dd), pending the issuance of regulations.

If to prevent an imminent hazard it becomes apparent that it is necessary for the proposed regulations to become effective immediately, USDA will utilize the provisions of 5 U.S.C. 553 which provide for the issuance of an interim rule, which would be effective upon publication, followed by a 60-day comment period.

Executive Order 12291 and Regulatory Flexibility Act

The proposed rule is issued in conformance with Executive Order 12291 and has been determined to be not a "major rule." Based on information compiled by the Department, it has been determined that this proposed rule would not have a significant effect on the economy; would not cause a major increase in costs or prices for consumers, individual industries, Federal, State, or local government agencies, or geographic regions; and would not have a significant adverse

effect on competition, employment, investment, productivity, innovation, or on the ability of United States-based enterprises to compete with foreign-based enterprises in domestic or export markets.

As explained above, the regulations regulate the introduction (importation, interstate movement, and release into the environment) of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests. Such organisms and products are deemed regulated articles for which a permit would have to be obtained prior to its introduction.

It is anticipated that the cost of preparing a permit application will cost no more than $5,000 per application. The required information about the organism, and the way it was altered or produced should be available from documents pertaining to the research and development of the regulated article. Thus, a person seeking to obtain a permit should not have to generate any new data, but rather submit to USDA, what should be, existing data. The $5,000 estimated cost is based on the salaries of a Ph.D. researcher and the necessary clerical staff working for approximately 2 weeks in preparing an application for a permit. During the first year, the Department does not expect to receive more than 50 applications. Most other costs associated with complying with the regulations, e.g., container requirements, are merely incidental to a person complying with sound laboratory and research practices. The only other costs associated with complying with the regulations would arise if a supplemental report were required if a regulated article dies, an accidental or unauthorized release of a regulated article, the regulated article is found to have substantially different charcteristics than those listed in the application, or the Deputy Administrator otherwise believes monitoring reports are required. It is anticipated that the cost of such reports in most instances would be minimal.

USDA is requiring that an application for a permit be submitted 180 days prior to the time a person seeks to introduce a regulated article. USDA believes that the 180 day time period required to process a permit application will not be an unreasonable delay in the marketing of organisms or products subject to regulations under Part 340. It is anticipated that if USDA receives only 50 applications, the average time to process any application will be considerably less than 180 days.

Since the timing of when to submit an application to USDA is left to an applicant, USDA believes that both large and small business entities will be able to incorporate the 180 day review period into their corporate planning process so as not to disrupt the marketing of organisms or products that are subject to regulation.

Under the circumstances referred to above, the Administrator of the Animal and Plant Health Inspection Service has determined that this action would not have a significant economic impact on a substantial number of small entities.

Paperwork Reduction Act

In accordance with section 3507 of the Paperwork Reduction Act of 1980 (44 U.S.C. 3507), the information collection provisions that are included in this proposed rule have been submitted for approval to the Office of Management and Budget (OMB). Written comments concerning any information collection provisions should be submitted to the Office of Information and Regulatory Affairs, OMB, Attention: Desk Officer for APHIS, Washington, DC 20503. A duplicate copy of such documents should be submitted to Dr. James W. Glosser, Associate Administrator, Animal and Plant Health Inspection Service, U.S. Department of Agriculture, Room 313–E, Administration Building, 14th and Independence Avenue, SW., Washington, DC 20250.

Executive Order 12372

This program/activity is listed in the Catalog of Federal Domestic Assistance under No. 10.025 and is subject to the provisions of Executive Order 12372 which requires intergovernmental consultation with State and local officials. (See 7 CFR Part 3015, Subpart V)

List of Subjects in 7 CFR Part 340

Agricultural Commodities, Plant diseases, Plant pests, Plants (agriculture), Quarantine, Transportation, Biotechnology, Genetic engineering.

PART 330—FEDERAL PLANT PEST REGULATIONS; GENERAL; PLANT PESTS; SOIL, STONE AND QUARRY PRODUCTS; GARBAGE

Accordingly, it is proposed to amend Title 7 of the Code of Federal Regulations as follows:

1. The authority citation for 7 CFR Part 330 would be revised to read as follows:

Authority: 7 U.S.C. 147a, 150bb, 150dd–150ff, 161, 162, 450, 2260; 19 U.S.C. 1306; 21 U.S.C. 111, 114a; 31 U.S.C. 9701; 42 U.S.C. 4331, 4332; 44 U.S.C. 3507; 7 CFR 2.17, 2.51, and 371.2(c).

2. The definition of "Plant Pest" in § 330.100(h) would be removed and the following new paragraphs (h)(1) and (h)(2) would be added to read as follows:

§ 330.100 [Amended]

* * * * *

(h)(1) *Plant pest.* Except for §§ 330.200–330.212, "Plant Pest" means any living stage of any insects, mites, nematodes, slugs, snails, protozoa, or other invertebrate animals, bacteria, fungi, other parasitic plants or reproductive parts thereof, viruses, or any organisms similar to or allied with any of the foregoing, or any infectious substances which can directly or indirectly injure or cause disease or damage in any plants or parts thereof, or any processed, manufactured, or other products of plants.

(2) *Plant pest.* For purposes of §§ 330.200–330.212, "Plant Pest" means any living stage of insects, mites, nematodes, slugs, snails, protozoa, or other invertebrate animals, bacteria, fungi, other parasitic plants or reproductive parts thereof, viruses, or any organisms similar to or allied with any of the foregoing, or any infectious substances which are not genetically engineered as defined in 7 CFR 340.1 which can directly or indirectly injure or cause disease or damage in any plants or parts thereof, or any processed, manufactured, or other products of plants.

3. Part 340 "Introduction of Organisms and Products Altered or Produced Through Genetic Engineering Which Are Plant Pests or Which There Is Reason to Believe Are Plant Pests" would be added to read as follows:

PART 340—INTRODUCTION OF ORGANISMS AND PRODUCTS ALTERED OR PRODUCED THROUGH GENETIC ENGINEERING WHICH ARE PLANT PESTS OR WHICH THERE IS REASON TO BELIEVE ARE PLANT PESTS [1]

Sec.

[1] Part 340 regulates the introduction of organisms altered or produced through genetic engineering and their products which are plant pests or which there is reason to believe are plant pests. The introductioninto the United States of such articles may be subject to other regulations promulgated under the Federal Plant Pest Act (7 U.S.C. 150aa *et seq.*), the Plant Quarantine Act (7 U.S.C. 151 *et seq.*) and the Federal Noxious Weed Act (7 U.S.C. 2801 *et seq.*) and found in 7 CFR Parts 319, 321, 330, and 360.

Authority: 7 U.S.C. 150aa–150jj, 151–167, 1622n; 31 U.S.C. 9701; 7 CFR 2.17, 2.51, and 371.2(c).

§ 340.0 Restrictions on the introduction of regulated articles.

(a) No person shall introduce any regulated article unless—

(1) Such introduction is authorized by a permit; and

(2) Such introductionis in conformity with all of the other applicable restrictions in this part.

(b) Any regulated article introduced not in compliance with the requirements of this part shall be subject to the immediate application of such remedial measures or safeguards against escape of plant pests as the inspector determines necessary to prevent the introduction of such plant pests.[2]

§ 340.1 Definitions.

Terms used in the singular form in this part shall be construed as the plural, and vice versa, as the case may demand. The following terms, when used in this part, shall be construed, respectively, to mean:

Certificate of exemption. A written certificate issued by the Deputy Administrator in accordance with § 340.4 of this part.

Classical genetics. Genetic manipulation of organisms by procedures which occur in nature or in conventional breeding, including but not restricted to such methods as natural or hand pollination and natural or artificial insemination and undirected mutagenesis.

Deputy Administrator. The Deputy Administrator for Plant Protection and Quarantine, Animal and Plant Health Inspection Service, U.S. Department of Agriculture, or any other officer or employee of the Department to whom authority to act in his/her stead has been or may hereafter be delegated.

Donor organism. The organism from which genetic material is obtained for transfer to the recipient organism.

Environment. All the land, air, and water; and all living organisms in association with land, air and water.

Genetic engineering. Genetic manipulation of organisms by procedures other than those used in classical genetics, including, but not limited to, protoplast, cell, and embryo fusion; and recombinant DNA engineering; and directed mutagenesis.

Genetic manipulation. The process of causing hereditary variation in an organism through the introduction of change in its DNA or RNA structure or function.

Inspector. Any employee of Plant Protection and Quarantine, Animal and Plant Health Inspection Service, U.S. Department of Agriculture, or other person, authorized by the Deputy Administrator in accordance with law to enforce the provisions of this part.

Interstate. From any State into or through any other State.

Introduce or introduction. To move into or through the United States, to release into the environment, to move interstate, or any attempt thereat.

Move (moving, movement). To ship, offer for shipment, offer for entry, import, receive for transportation, carry, or otherwise transport or move, or allow to be moved into, through, or within the United States.

Mutagen. Agents such as colchicine, radioactive elements, lasers, and ultraviolet light that cause mutations without the exchange of genetic material between organisms.

Organism. Any active, infective, or dormant stage or life form of an entity characterized as living, including vertebrate and invertebrate animals, plants, bacteria, fungi, mycoplasmas, mycoplasma-like organisms, as well as entities such as viroids, viruses, and prions, or any entity related to the foregoing; and any part, copy, or analog thereof, including DNA and RNA, which is infectious.

Pathogen. A virus or microorganism (including its viruses and plasmids, if any) that has the ability to cause disease in other living organisms. Excluded are those microorganisms for which it can be documented that the microorganisms come from nonpathogenic species (e.g., *Bacillus subtilis, Lactobacillus acidophilus,* and *Saccharomyces* species) or come from a nonpathogenic strain of a pathogenic species (e.g., *Escherichia coli,* K–12).

Permit. A written permit issued by the Deputy Administrator for the introduction of a regulated article under conditions determined by the Deputy Administrator not to present a risk of plant pest introduction.

Person. Any individual, partnership, corporation, company, society, association, or other organized group.

Plant. Any living stage or form of any organism of the plant kingdom including, but not limited to, bacteria, prokaryotic algae, eukaryotic algae, fungi, mosses, club mosses, ferns, horsetails, liverworts, angiosperms, gymnosperms, and lichens (which contain algae) including any parts (e.g. pollen, seeds, cells, tubers, stems) thereof, and any cellular components (e.g. plasmids, ribosomes, etc.) thereof.

Plant pest. Any living stage (including active and dormant forms) of insects, mites, nematodes, slugs, snails, protozoa, or other invertebrate animals, bacteria, fungi, other parasitic plants or reproductive parts thereof; viruses; or any organisms similar to or allied with any of the foregoing; or any infectious agents or substances, which can directly or indirectly injure or cause disease or damage in or to any plants or parts thereof, or any processed, manufactured, or other products or plants.

Plant Protection and Quarantine. The organizational unit within the Animal and Plant Health Inspection Service, U.S. Department of Agriculture, delegated responsibility for enforcing provisions of the Plant Quarantine Act, the Federal Plant Pest Act, and related legislation, and quarantine and regulations promulgated thereunder.

Product. Anything made by or from, or derived from an organism, living or dead.

Recipient organism. The organism which receives genetic material from a donor organism.

Regulated article. Any organism or product which has been altered or produced through genetic engineering, if the donor organism, recipient organism, or vector or vector agent belongs to a group designated in § 340.2 of this part, or any organism or product altered or produced through genetic engineering which the Deputy Administrator determines is a plant pest or has reason to believe is a plant pest. Excluded are microorganisms that are non-pathogenic, non-infectious, and otherwise not plant pests, that have resulted from the addition of genetic material that is well characterized and contains only non-coding regulatory regions (i.e. operators, promoters, origins of replication, terminators, and ribosome binding regions).

Release into environment. The use of a regulated article outside the constraints of physical confinement that are found in a laboratory, contained greenhouse, or a fermenter or other contained structure.

[2] Pursuant to section 105 of the Federal Plant Pest Act (7 U.S.C. 150dd) the Secretary of Agriculture is authorized to order prompt removal from the United States or to seize, quarantine, treat, apply other remedial measures to, destroy, or otherwise dispose of, in such manner as the Secretary deems appropriate, certain regulated articles which are believed to be infested or infected by or contains a plant pest.

Responsible person. The person who has control and will maintain control over the introduction of the regulated article and assure that all conditions contained in the permit and requirements in this part are complied with. A responsible person shall be a resident of the United States or designate an agent who is a resident of the United States.

Secretary. The Secretary of Agriculture, or any other officer or employee of the Department of Agriculture to whom authority to act in his/her stead has been or may hereafter be delegated.

State. Any State, District of Columbia, American Samoa, Guam, Northern Mariana Islands, Puerto Rico, the Virgin Islands of the United States, and any other Territories or Districts of the United States.

United States. All of the States.

Vector or vector agent. Organisms or objects used to transfer genetic material from the donor organism to the recipient organism.

Well-characterized and contains only non-coding regulatory regions (i.e. operators, promoters, origins of replication, terminators, and ribosome binding regions). The genetic material added to a microorganism in which the following can be documented about such genetic material:

(a) The exact nucleotide base sequence of the regulatory region and any inserted flanking nucleotides;

(b) The regulatory region and any inserted flanking nucleotides do not code for protein or peptide; and

(c) The regulatory region solely controls the activity of other sequences that code for protein or peptide molecules or act as recognition sites for the initiation of nucleic acid or protein synthesis.

§ 340.2 Groups of organisms which are or contain plant pests.

The organisms that are or contain plant pests are included in taxa or groups in the classification scheme below. Within each taxon or group all organisms are considered to be plant pests unless there are included taxa or groups of lower rank specifically listed, in which instance only those taxa or groups of lower rank specifically listed are considered to be plant pests or contain plant pests.

Note.—Any genetically engineered organism composed of DNA or RNA sequences, organelles, plasmids, parts, copies, and/or analogs, of or from any of the groups of organisms listed below shall be deemed a regulated article.

Group and Common Name

Viroids
Prions

Superkingdom Prokaryotae

Kingdom Virus

All members of groups containing plant viruses, and all other plant and insect viruses.

Kingdom Monera

Division Bacteria

Bacteria that are pathogenic to insects:
Family Pseudomonadaceae
Genus Pseudomonas—pseudomonads
Genus Xanthomonas—xanthomonads
Family Rhizobiaceae
Genus Rhizobium—rhizobia
Genus Bradyrhizodium—bradyrhizobia
Genus Agrobacterium—crown gall
Genus Phyllobacterium
Family Enterobacteriaceae
Genus Erwinia—soft rot bacteria
Family Streptomycetaceae
Genus Streptomyces
Family Actinomycetacease
Genus Actinomyces
Coryneform group
Genus Clavibacter
Genus Arthrobacter
Genus Curtobacterium
Genus Corynebacteria—plant pathogenic corynebacteria
Rickettsiaceae
Rickettsial-like organisms associated with plant diseases
Rickettsial-like organisms associated with insect diseases
Class Mollicutes
Order Mycoplasmatales
Family Spiroplasmataceae
Genus Spiroplasma
Mycoplasma-like organisms associated with plant diseases
Mycoplasma-like organisms associated with insect diseases

Superkingdom Eukaryotae

Kingdom Plantae

Subkingdom Thallobionta

Division Cholorophyta—green algae
Genus Cephaleuros—parasitic algae
Genus Rhodochytrium—parasitic algae
Genus Phyllosiphon—parasitic algae
Division Myxomycota
Class Plasmodiophoromycetes—plasmodiophorids
Division Eumycota—true fungi
Fungi associated with diseases of insects
Class Chytridiomycetes
Order Chytridiales
Class Oomycetes
Order Lagenidiales
Family Lagenidiaceae
Family Olpidiopsidaceae
Order Peronosporales
Family Albuginaceae
Family Peronosporaceae
Family Pythiaceae
Order Saprolegniales
Family Saprolegniaceae
Family Leptolegniellaceae
Class Zygomycetes
Order Mucorales
Family Choanephoraceae
Family Mucoraceae
Family Entomophthoraceae
Class Hemiascomycetes
Family Protomycetaceae
Family Taphrinaceae
Class Loculoascomycetes
Order Myriangiales
Family Elsinoeaceae
Family Myriangiaceae
Order Asterinales
Order Dothideales
Order Chaetothyriales
Order Hysteriales
Family Parmulariaceae
Family Phillipsiellaceae
Family Hysteriaceae
Order Pleosporales
Order Melanommatales
Class Plectomycetes
Order Eurotiales
Family Ophiostomataceae
Order Ascophaerales
Class Pyrenomycetes
Order Erysiphales
Order Meliolales
Order Xylariales
Order Diaporthales
Order Hypocreales
Order Clavicipitales
Class Discomycetes
Order Phacidiales
Order Helotiales
Family Ascocorticiaceae
Family Hemiphacidiaceae
Family Dermataceae
Family Sclerotiniaceae
Order Cytarriales
Order Medeolariales
Order Pezizales
Family Sarcosomataceae
Family Sarcoscyphaceae
Class Teliomycetes
Class Phragmobasidiomycetes
Family Auriculariaceae
Family Ceratobasidiaceae
Class Hymenomycetes
Order Exobasidiales
Order Agaricales
Family Corticiaceae
Family Hymenochaetaceae
Family Echinodontiaceae
Family Fistulinaceae
Family Clavariaceae
Family Polyporaceae
Family Tricholomataceae
Class Hyphomycetes
Class Coelomycetes

Subkingdom Embryobionta

Note: *Organisms listed in the Code of Federal Regulations as noxious weeds are regulated under the Federal Noxious Weeds Act.*

Division Magnoliophyta—angiosperms
Family Balanophoraceae—parasitic species
Family Cuscutaceae—parasitic species
Family Hydnoraceae—parasitic species
Family Krameriaceae—parasitic species
Family Lauraceae—parasitic species
Genus Cassytha
Family Lennoaceae—parasitic species
Family Loranthaceae—parasitic species
Family Myzodendraceae—parasitic species
Family Olacaceae—parasitic species
Family Orobanchaceae—parasitic species
Family Rafflesiaceae—parasitic species
Family Santalaceae—parasitic species
Family Scrophulariaceae—parasitic species
Genus Alectra
Genus Bartsia

Genus Buchnera
Genus Buttonia
Genus Castilleja
Genus Centranthera
Genus Cordylanthus
Genus Dasistoma
Genus Euphrasia
Genus Gerardia
Genus Harveya
Genus Hyobanche
Genus Lathraea
Genus Melampyrum
Genus Melasma
Genus Orthantha
Genus Orthocarpus
Genus Pedicularis
Genus Rhamphicarpa
Genus Rhinanthus
Genus Schwalbea
Genus Seymeria
Genus Siphonostegia
Genus Sopubia
Genus Striga
Genus Tozzia
Family Viscaceae—parasitic species

Kingdom Animalia

Subkingdom Protozoa

Protozoa associated with insect diseases
Genus Phytomonas—protozoa

Subkingdom Eumetazoa

Phylum Nemata
Nematodes that are predaceous on insects or are associated with insect diseases
Class Secernentea
Order Tylenchida
Family Anguinidae
Family Belonolaimidae
Family Caloosiidae
Family Criconematidae
Family Dolichodoridae
Family Fergusobiidae
Family Hemicycliophoridae
Family Heteroderidae
Family Hoplolaimidae
Family Meloidogynidae
Family Nacobbidae
Family Neotylenchidae
Family Nothotylenchidae
Family Paratylenchidae
Family Pratylenchidae
Family Tylenchidae
Family Tylenchulidae
Order Aphelenchida
Family Adhelenchoididae
Class Adenophorea
Order Dorylaimida
Family Longidoridae
Family Trichodoridae
Phylum Mollusca
Class Gastropoda—snails and slugs
Subclass Pulmonata
Order Basommatophora
Superfamily Planorbacea
Family Succineidae
Superfamily Achatinacae
Superfamily Arionacae
Superfamily Limacacea
Superfamily Helicacea
Order Stylommatophora
Subfamily Strophocheilacea
Family Succineidae
Superfamily Achatinacae
Superfamily Arionacae
Superfamily Limacacea
Superfamily Helicacea
Order Systellommatophora
Superfamily Veronicellacea
Phylum Arthropoda
Class Arachnida
Order Parasitiformes
Suborder Mesostigmata
Superfamily Ascoidea
Superfamily Dermanyssoidea
Order Acariformes
Suborder Prostigmata
Superfamily Eriophyoidea—gall mites
Superfamily Tetranychoidea
Superfamily Eupodoidea
Superfamily Tydeoidea
Superfamily Erythraenoidea
Superfamily Trombidioidea
Superfamily Hydryphantoidea
Superfamily Tarsonemoidea
Superfamily Pyemotoidea
Suborder Astigmata
Superfamily Hemisarcoptoidea
Superfamily Acaroidea
Class Diplopoda
Order Polydesmida—millipedes
Class Insecta
Order Collembola
Family Sminthoridae—springtails
Order Isoptera—termites
Order Thysanoptera—thrips
Order Orthoptera
Family Acrididae—short-horned grasshoppers
Family Gryllidae—crickets
Family Gryllacrididae—leaf-rolling crickets
Family Gryllotalpidae—mole crickets
Family Phasmatidae—walking sticks
Family Ronaleidae
Family Tettigoniidae—longhorned grasshoppers
Family Tetrigidae—tetrigoids
Order Hemiptera
Family Thaumastocoridae
Family Aradidae
Superfamily Piesmatoidea
Superfamily Lygaeoidea
Superfamily Idiostoloidea
Superfamily Coreoidea
Superfamily Pentatomoidea
Superfamily Pyrrhocoroidea
Superfamily Tingoidea
Superfamily Miroidea
Order Homoptera
Order Coleoptera
Family Anobiidae—anoibiids
Family Apionidae—apionids
Family Anthribidae—seed weevils
Family Bostrichidae—twig borers
Family Brentidae—straight-snouted beetles
Family Bruchidae—seed beetles
Family Buprestidae—flatheaded wood borers
Family Byturidae—fruitworm beetles
Family Cantharidae—soldier beetles
Family Carabidae—ground beetles
Family Cerambycidae—long-horned beetles
Family Chrysomelidae—leaf and flea beetles
Family Coccinellidae—ladybird beetles
Subfamily Epilachninae
Family Curculionidae—weevils
Family Dermestidae—skin & carpet beetles
Family Elateridae—click beetles
Family Hydrophilidae
Genus Helophorus
Family Lyctidae—powder-post beetles
Family Meloidae—blister beetles
Family Mordellidae—tumbling flower beetles
Family Platypodidae—pin-hole borers
Family Scarabaeidae
Subfamily Melolonthinae—June beetles
Subfamily Rutelinae—chafers
Subfamily Cetoniinae—flower beetles
Subfamily Dynastinae—rhinoceros beetles
Family Scolytidae—bark beetles
Family Seblytidae—bark beetles
Family Tenebrionidae—darkling beetles
Order Lepidoptera
Order Diptera
Family Agromyzidae—leafminers
Family Anthomyiidae—rootmaggot flies
Family Cecidomyiidae—gall midges, gnats
Family Chloropidae—chloropod flies
Family Ephydridae—shore flies
Family Lonchaeidae—lonchaeid flies
Family Muscidae—muscid flies
Genus Atherigona
Family Otitidae—picture-winged flies
Genus Euxeta
Family Syrphidae—flower flies
Family Tephritidae—fruit flies
Family Tipulidae—crane flies
Order Hymenoptera
Family Apidae—bees
Family Cephidae—stem sawflies
Family Chalcidae—chalcids
Family Cynipidae—gall wasps
Family Eurytomidae—seed chalcids
Family Formicidae—ants
Family Psilidae—rust flies
Family Siricidae—horntails
Family Tenthredinidae—sawflies
Family Torymidae—tormids
Family Xylocopidae—carpenter bees

Unclassified organisms and/or organisms whose classification is unknown.

§ 340.3 Permits.

(a) *Application for permit.* A written application for a permit to introduce a regulated article shall be submitted by

the responsible person on an application form obtained from Plant Protection and Quarantine, to the Biological Assessment Support Staff, Plant Protection and Quarantine, Animal and Plant Health Inspection Service, U.S. Department of Agriculture, Federal Building, 6505 Belcrest Road, Hyattsville, Maryland 20782. The application shall be submitted at least 180 days in advance of the proposed introduction and shall include the following information:[3]

(1) Name, title, address, telephone number, signature of the responsible person and type of permit requested (for importation, interstate movement, or release into the environment);

(2) All scientific, common, and trade names, and all designations necessary to identify the: donor organism; recipient organism; vector or vector agent; constituent of each regulated article which is a product; and, regulated article;

(3) Names, addresses, and telephone numbers of the persons who developed and/or supplied the regulated article;

(4) A description of the means of movement, e.g., mail, freight, baggage, or handcarried (and by whom);

(5) A description of the anticipated or actual expression of the altered genetic material in the regulated article and how that expression differs from the expression in the non-modified parental organism (e.g., morphological or structural characteristics, physiological activities and processes, number of copies of inserted genetic material and the physical state of this material inside the recipient organism (integrated or extrachromosomal), products and secretions, growth characteristics);

(6) A detailed description of the molecular biology of the system (e.g., donor-recipient-vector) which is or will be used to produce the regulated article;

(7) Country and locality where the donor organism, recipient organism, vector or vector agent, and regulated article were collected, developed, and produced;

(8) A detailed description of the purpose for the introduction of the regulated article including a detailed description of the proposed experimental and/or production design;

(9) The quantity of the regulated article to be introduced and proposed schedule and number of introductions;

(10) A detailed description of the processes, procedures, and safeguards which have been used or will be used in the country of origin and in the United States to prevent contamination, release, and dissemination in the production of the: donor organism; recipient organism; vector or vector agent; constituent of each regulated article which is a product; and, regulated article;

(11) A detailed description of the intended destination (including final and all intermediate destinations), uses, and/or distribution of the regulated article (e.g., greenhouses, laboratory, or growth chamber location; field trail location; pilot project location; production, propogation, and manufacture location; proposed sale and distribution location);

(12) A detailed description of the proposed procedures, processes, and safeguards which will be used to prevent escape and dissemination of the regulated article at each of the intended destinations;

(13) A detailed description of any biological material (e.g., culture medium, or host material) accompanying the regulated article during movement; and

(14) A detailed description of the proposed method of final disposition of the regulated article.

(b) *Administrative action on applications.* After receipt and review by Plant Protection and Quarantine of the application and the data submitted pursuant to paragraph (a) of this section, including any additional information requested by Plant Protection and Quarantine, a permit shall be granted or denied. If a permit is denied, the applicant shall be promptly informed of the reasons why the permit was denied. If a permit is granted, the permit will specify the applicable conditions for introduction of the regulated article under this part.

(c) *Permit conditions.* A person who is issued a permit and his/her agents shall comply with the following conditions, and any supplemental conditions which shall be listed on the permit, as deemed by the Deputy Administrator to be necessary to prevent the introduction of plant pests:

(1) The regulated article shall be maintained and disposed of (when necessary) in a manner determined necessary by the Deputy Administrator;

(2) All packing material, shipping containers, and any other material accompanying the regulated article shall be treated or disposed of as determined necessary by the Deputy Administrator;

(3) The regulated article shall be kept separate from other organisms, except as specifically allowed in the permit;

(4) The regulated article shall be maintained only in areas and premises specified in the permit;

(5) An inspector shall be allowed access, during regular business hours, to the place where the regulated article is maintained;

(6) The regulated article shall, when possible, be kept identified with a label showing the name of the regulated article, and when applicable, the port accession number and date of importation;

(7) The regulated article shall be subject to the application of measures determined by the Deputy Administrator to be necessary to prevent the accidential or authorized release of the regulated article;

(8) The regulated article shall be subject to the application of remedial measures (including disposal) determined by the Deputy Administrator to be necessary to prevent the spread of plant pests;

(9) A person who has been issued a permit shall submit to Plant Protection and Quarantine monitoring reports on the performance characteristics of the regulated article, as deemed necessary by the Deputy Administrator;

(10) Plant Protection and Quarantine shall be orally notified immediately, and in writing, within the time periods specified below, in the event of the following occurrences:

(i) Within 24 hours in the event of any accidental or unauthorized release of the regulated article;

(ii) Within 5 working days if the regulated article is found to have characteristics substantially different from those listed in the application for a permit; and

(iii) Within 5 working days if the regulated article dies.

(11) A permittee or his/her agent who seeks to import a regulated article into the United States shall:

(i) Import or offer the regulated article for entry only at a port of entry which is designated by an asterisk in 7 CFR 319.37–14(b);

(ii) Notify Plant Protection and Quarantine promptly upon arrival of any regulated article at a port of entry, of its arrival by such means as a manifest, customs entry document, commercial invoice, waybill, a broker's document, or a notice form provided for such purpose; and

(iii) Mark and identify the regulated article in accordance with § 340.5 of this part.

[3] Application forms are available without charge from the Biological Assessment Support Staff, Plant Protection and Quarantine, Animal and Plant Health Inspection Service, U.S. Department of Agriculture, Federal Building, 6505 Belcrest Road, Hyattsville, Maryland 20782, or from local offices which are listed in telephone directories. A person should specify in requesting the application that the permit is for the introduction of a regulated article subject to regulation under Part 340.

(d) *Withdrawal of a permit.* Any permit which has been issued may be withdrawn by an inspector or the Deputy Administrator if he/she determines that the holder thereof has not complied with one or more of the conditions listed on the permit. The reasons for the withdrawal shall be confirmed in writing as promptly as circumstances allow. Any person whose permit has been withdrawn may appeal the decision in writing to the Deputy Administrator within ten (10) days after receiving the written notification of the withdrawal. The appeal shall state all of the facts and reasons upon which the person relies to show that the permit was wrongfully withdrawn. The Deputy Administrator shall grant or deny the appeal, in writing, stating the reasons for the decision as promptly as circumstances allow. If there is a conflict as to any material fact, a hearing shall be held to resolve such conflict. Rules of practice concerning such a hearing will be adopted by the Administrator.

§ 340.4 Certificate of exemption.

(a) *Issuance.* The Deputy Administrator may issue a certificate of exemption for the introduction of organisms modified through biotechnology which are not subject to regulation under this part to facilitate movement when the movement might otherwise be impeded because of the similarity of the organism to other organisms regulated under this part.

(b) *Application.* A person seeking a certificate of exemption shall submit on an application form obtained from Plant Protection and Quarantine data required by § 340.3(a) (1), (2), and (5) of this part and shall indicate such data is being submitted as a request for a certificate of exemption. A person should also include a statement explaining why he or she believes the organism or product is not a plant pest.

§ 340.5 Marking and identity.

(a) Any regulated article to be imported other than by mail, shall, at the time of importation into the United States, plainly and correctly bear on the outer container the following information:

(1) General nature and quantity of the contents;

(2) Country and locality where collected, developed, manufactured, reared, cultivated or cultured;

(3) Name and address of shipper, owner, or person shipping or forwarding the organism;

(4) Name, address, and telephone number of consignee;

(5) Identifying shipper's mark and number; and

(6) Number of written permit authorizing the importation.

(b) Any regulated article imported by mail, shall be plainly and correctly addressed and mailed to Plant Protection and Quarantine at a port of entry designated by an asterisk in 7 CFR 319.37–14(b) and shall be accompanied by a separate sheet of paper within the package plainly and correctly bearing the name, address, and telephone number of the intended recipient, and shall plainly and correctly bear on the outer container the following information:

(1) General nature and quantity of the contents;

(2) Country and locality where collected, developed, manufactured, reared, cultivated, or cultured;

(3) Name and address of shipper, owner, or person shipping or forwarding the regulated article; and

(4) Number of permit authorizing the importation.

(c) Any regulated article imported into the United States by mail or otherwise, shall at the time of importation or offer for importation into the United States, be accompanied by an invoice or packing list indicating the contents of the shipment.

§ 340.6 Container requirements for the movement of regulated articles.[4]

(a) *General requirements.* A regulated article shall not be moved unless it complies with the provisions of paragraph (b) of this section.

(b) *Container requirements.*—(1) *Plants and plant parts.* All plants or plant parts, except seeds, cells, and subcellular elements shall be packed in a sealed plastic bag of at least 5 mil thickness, inside a sturdy, sealed, leak-proof, outer shipping container constructed of corrugated fiberboard, corrugated cardboard, wood, or other material of equivalent strength.

(2) *Seeds.* All seeds shall be transported in a sealed plastic bag of at least 5 mil thickness, inside a sealed metal container, which shall be placed inside a second sealed metal container. Shock absorbing cushioning material shall be placed between the inner and outer metal containers. Each metal container shall be independently capable of protecting the seeds and preventing spillage or escape. Each set of metal containers shall then be enclosed in a sturdy outer shipping container constructed of corrugated fiberboard, corrugated cardboard, wood, or other material of equivalent strength.

(3) *Live microorganisms and/or etiologic agents, cells, or subcellular elements.* All regulated articles which are live (non-inactivated) microorganisms, or etiologic agents, cells, or subcellular elements shall be packed as specified below:

(i) *Volume not exceeding 50 ml.* Regulated articles not exceeding 50 ml. shall be placed in a securely closed, watertight container (primary container (test tube, vial, etc.)) which shall be enclosed in a second, durable watertight container (secondary container). Several primary containers may be enclosed in a single secondary container, if the total volume of all the primary containers so enclosed does not exceed 50 ml. The space at the top, bottom, and sides between the primary and secondary containers shall contain sufficient nonparticulate absorbent material (e.g., paper towel) to absorb the entire contents of the primary container(s) in case of breakage of leakage. Each set of primary and secondary containers shall then be enclosed in an outer shipping container constructed of corrugated fiberboard, corrugated cardboard, wood, or other material of equivalent strength.

(ii) *Volume greater than 50 ml.* Regulated articles which exceed a volume of 50 ml. shall comply with requirements specified in paragraph (b)(3)(i) of this section. In addition, a shock absorbing material, in volume at least equal to that of the absorbent material between the primary and secondary containers, shall be placed at the top, bottom, and sides between the secondary container and the outer shipping container. Single primary containers shall not contain more than 1,000 ml. of material. However, two or more primary containers whose combined volumes do not exceed 1,000 ml. may be placed in a single, secondary container. The maximum amount of microorganisms or etiologic agents, cells, or subcellular elements which may be enclosed within a single outer shipping container shall not exceed 4,000 ml.

(iii) *Dry ice.* If dry ice is used as a refrigerant, it shall be placed outside the secondary container(s). If dry ice is used between the secondary container and the outer shipping container, the shock absorbing material shall be placed so that the secondary container does not become loose inside the outer shipping container as the dry ice sublimates.

[4] The requirements of this section are in addition to and not in lieu of any other packing requirements such as those for the transportation of etiologic agents prescribed by the Department of Transportation in Title 49 of the Code of Federal Regulations or any other agency of the Federal government.

(4) *Insects, mites, and related organisms.* Insects, mites, and other small arthropods shall be packed for shipment as specified in this section or in paragraph (b)(3) of this section. Insects (any life stage) shall be placed in an escape-proof primary shipping container (insulated vacuum container, glass, metal, plastic, etc.) and sealed to prevent escape. Such primary container shall be placed securely within a secondary shipping container of crushproof styrofoam or other material of equivalent strength; one or more rigid ice packs may also be placed within the secondary shipping container; and sufficient packing material shall be added around the primary container to prevent movement of the primary shipping container. The secondary (styrofoam or other) container shall be placed securely within an outer shipping container constructed of corrugated fiberboard, corrugated cardboard, wood, or other material of equivalent strength.

(5) *Other macroscopic organisms.* Other macroscopic organisms not covered in paragraphs (b) (1), (2), and (4) of this section which do not require continuous access to atmospheric oxygen shall be packaged as specified in paragraphs (b) (3) or (4) of this section. All macroscopic organisms which are not plants and which require continuous access to atmospheric oxygen shall be placed in primary shipping containers constructed of a sturdy, crush-proof frame of wood, metal, or equivalent strength material, surrounded by escape-proof mesh or netting of a strength and mesh size sufficient to prevent the escape of the smallest organism in the shipment, with edges and seams of the mesh or netting sealed to prevent escape of organisms. Each primary shipping container shall be securely placed within a larger secondary shipping container constructed of wood, metal, or equivalent strength material. The primary and secondary shipping containers shall then be placed securely within an outer shipping container constructed of corrugated fiberboard, corrugated cardboard, wood, or other material of equivalent strength, which outer container may have air holes or spaces in the sides and/or ends of the container, provided that the outer shipping container must retain sufficient strength to prevent crushing of the primary and secondary shipping containers.

§ 340.7 Cost and charges.[5]

The services of the inspector during regularly assigned hours of duty and at the usual places of duty shall be furnished without cost.[5] The U.S. Department of Agriculture will not be responsible for any costs or charges incident to inspections or compliance with the provisions of this part, other than for the services of the inspector.

Done at Washington, DC, this 23rd day of May 1986.

Harvey L. Ford,

Deputy Administrator, Plant Protection and Quarantine, Animal and Plant Health Inspection Service.

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[5] The Department's provisions relating to overtime charges for an inspector's services are set forth in 7 CFR Part 354.